MIXED METHODS RESEARCH DESIGN TO DETERMINE CLINICAL CHARACTERISTICS, CONTRIBUTORY FACTORS AND PATIENTS' PERCEPTIONS OF FATIGUE IN INFLAMMATORY ARTHRITIS

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DECLARATION

I hereby declare that this thesis has not been submitted as an exercise for a degree at this or any other university and that it is entirely my own work.

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SUMMARY

BACKGROUND: Fatigue is an important symptom in inflammatory arthritis, however, its utility as an outcome measure is not universally accepted and intervention is seldom considered. The purpose of this mixed methods study was to determine the clinical characteristics of, contributory factors to, and unexplained elements of, fatigue in patients with inflammatory arthritis from a clinical and patient perspective; to determine a basis for standardisation of measurement, and possible intervention in clinical practice.

METHODS: Firstly, a longitudinal, descriptive study of fatigue was undertaken. Successive patients with active rheumatoid arthritis (RA) and psoriatic arthritis (PsA) commencing TNFi therapy underwent standard clinical assessments of disease activity using the American College of Rheumatology (ACR) six core measures; 28-swollen and tender joint count; pain; global health; HAQ-disability index, and C-reactive protein, with fatigue as an additional assessment, using two fatigue scales (single item verbal rating scale (VRS); multidimensional assessment of fatigue scale (MAF)), at baseline, 3 and 6-months; the relationship between fatigue and the core measures was examined. Treatment response according to the Disease Activity Score 28 (DAS28), derived from the ACR core set, classified patients as good, moderate, or non-responders. Secondly, a comparative study of persistent post-treatment fatigue, was undertaken on two subgroups of patients with good disease response and either i) poor or ii) good fatigue outcome. This postal survey, of the larger RA cohort, used validated questionnaires: Short Form McGill pain questionnaire; Pittsburgh Sleep Quality Index; Profile of Mood Scale, Beck Depression Inventory and Beck Hopelessness Scale; Arthritis Self-Efficacy Scales, to capture information on possible contributory factors to fatigue. Finally, a qualitative study explored patients' experiences of persistent post treatment fatigue using semi-structured interviews and inductive content analysis. Partial mixing of methods was used throughout; setting objectives; participant selection; data integration through inference and narration.

RESULTS: Baseline, 3 month and 6 month assessments were completed by 130, 112 and 87 patients, respectively. At baseline 77% had moderate/very severe fatigue and 93% a moderate/high DAS28 score. Significant falls in fatigue levels, regardless of scale used (ANOVA $p<0.001$), and in all core outcome measures (ANOVA $p<0.001$) occurred in parallel following treatment initiation, at 3, and 6-months. At baseline, 3 and 6-months moderate or greater fatigue was reported by 77%, 48%, 46%, while at 3 and 6 months

43%, 40% were ‘moderate’, and 42%, 60% were ‘good’ EULAR disease responders, respectively. On multiple regression analysis, significant predictors of current fatigue changed with disease status over time; baseline, HAQ, global health and CRP; 3-months, pain and tender joint count; 6-months, global health. The only significant predictors of change in fatigue at 3-months were change in the HAQ-disability index and global health; there was no significant predictor of fatigue at 6-months. Overall, fatigue was largely unexplained (79-91%) by the core outcome measures.

In the second component of study patients with persistent fatigue despite good disease outcome had significantly higher RF incidence, DAS28, EMS duration and experienced more pain (p=0.02-0.009), but had less incidence of ever failing DMARDS and had lower self-efficacy for ‘other symptom’ management (p=0.022), than those with good fatigue outcome. Both patient groups experienced poor sleep quality (PSQI>5).

On qualitative study fatigue in RA emerged as an independent outcome, often not alluded to, amenable to measurement and intervention, abstracted from four major categories, i) fatigue as a unique symptom of RA, ii) plausible causes of fatigue, iii) fatigue as an incapacitating state, and iv) managing fatigue. Fatigue scales’ psychometric properties were upheld; the MAF demonstrated superior sensitivity to change. **CONCLUSION:** The hypothesis that fatigue is an important symptom in inflammatory arthritis that is partially influenced by disease status, and itself influences patient outcome, was supported. New evidence on sensitivity to change, and superiority of the MAF to VRS in detecting change in core set variables was provided, following a treatment intervention. While the influence exerted by the RA core outcomes measures on fatigue changed over time; fatigue was only partially explained by these variables, confirming fatigue’s unique contribution to outcome assessment. Evaluation of persistent fatigue highlighted potential modifiable factors to improve disease outcome; its association with characteristics of poor disease outcome; the need for optimal and judicious disease management, and professional recognition of fatigue; scope for and suitability of fatigue for assessment, in order to enhance the effective management of all symptoms, including fatigue, and therefore overall disease outcome.

DEDICATION

TO THE MEMORY OF BARRY BRESNIHAN,

A TRUE LEADER

A PERFECT MENTOR AND FRIEND

YOU ARE GREATLY MISSED

THANK YOU

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TABLE OF CONTENTS

LIST OF APPENDICES

TABLE OF TABLES

TABLE OF FIGURES

Chapter 1 Introduction: Fatigue in Inflammatory Arthritis

1.1 Fatigue in Inflammatory Arthritis

Fatigue is important as an outcome measure in inflammatory rheumatic disease because those with the disease have identified it as a salient symptom for which a therapeutic intervention is seldom advised or available (Tack 1990a' p 145.; Hewlett *et al.* 2005b; Repping-Wuts *et al.* 2007; Repping-Wuts *et al.* 2008a; Repping-Wuts *et al.* 2008b). Moreover, both patients and clinicians alike recognise fatigue as an important symptom in inflammatory arthritis, even though the rheumatology literature shows how patients and clinicians traditionally hold different perspectives on other outcomes in arthritis such as pain, global health and function (Carr *et al.* 2003; Kirwan *et al.* 2003; Sanderson *et al.* 2010). Fatigue associated with inflammatory arthritis, namely, rheumatoid arthritis and psoriatic arthritis, is a common and frequently very enduring symptom reported by patients (Wolfe *et al.* 1996; Schentag *et al.* 2000; American College of Rheumatology 2010). The estimated prevalence of clinically meaningful fatigue in patients with rheumatoid arthritis is 80-93%. Fatigue is likely to be comprised of more than one cause and component, and is therefore regarded as a multidimensional symptom (Wolfe *et al.* 1996; Repping-Wuts *et al.* 2004; Hewlett *et al.* 2005b; Mease *et al.* 2005a; Husted *et al.* 2009). Despite its ever-present nature, this symptom is still regarded as being poorly understood both by those with the disease (Hewlett *et al.* 2005b), and by professionals caring for them (Rasker 2009).

For these reasons, patients with rheumatoid arthritis and psoriatic arthritis have nominated fatigue as an important outcome measure (Hewlett *et al.* 2005b; Gladman *et al.* 2007b; Kirwan and Hewlett 2007). It was proposed that fatigue should be added to the existing 7-core set of outcome measures for rheumatoid arthritis for inclusion in all clinical trials and clinical studies (Felson *et al.* 1993; Kirwan *et al.* 2007). More recently, it received international endorsement as a patient centered outcome measure for inclusion in all studies on patients with rheumatoid arthritis (Aletaha *et al.* 2008).

Fatigue was also chosen as a core domain necessary to evaluate patients with psoriatic arthritis in clinical trials, longitudinal studies and rehabilitation (Gladman *et al.* 2007b). There is agreement between patients, clinicians and researchers that fatigue assessment would aid understanding of this symptom in patients with psoriatic arthritis. In turn, increased understanding would assist in the treatment and management of this major symptom (Kirwan *et al.* 2005b).

Since highlighted as a variable of interest in inflammatory arthritis, researchers, clinicians and patients delineated a research agenda on measuring and understanding fatigue in rheumatoid arthritis. Topics included: i) the development, validation and standardisation of appropriate measurement instruments for this complex multi-dimensional concept, ii) further clarification of the nature of the interrelationship between fatigue and other outcomes of the disease process; iii) evaluation of the consequences of fatigue; iv) temporal variations and patterns in fatigue; v) interventions to reduce fatigue, including pharmacological, and non-pharmacological supportive/complex interventions (Kirwan *et al.* 2007).

Similar research topics have been adopted, by and large, by expert groups on the disease entity of psoriatic arthritis. Research areas prioritised in relation to fatigue and psoriatic arthritis include i) the identification of the relationship between pain and fatigue and, ii) determination of the best instrument to measure fatigue (Gladman *et al.* 2007b).

1.2 Related Literature

The earliest studies on fatigue in rheumatoid arthritis include the seminal descriptive exploratory studies published by Tack (1990a, 1990b). These triangulated quantitative and qualitative data for the purpose of describing the multidimensional nature of fatigue, examining this symptom (Tack 1990b), and describing the prevalence, impact on health visits, and correlates of fatigue, while developing and testing the multidimensional assessment of fatigue (MAF) scale (Belza *et al.* 1993). The validity of this scale was also examined in a later prospective repeated measures study which compared self-reports of fatigue between patients with rheumatoid arthritis and controls (Belza 1995). The more

recent studies of the last decade are in keeping with the recommended research agenda (Kirwan *et al.* 2007). These can be grouped into five broad categories: i) the measurement of fatigue and validation of instruments, ii) relationship between fatigue and demographic variables such as gender and disease duration, iii) biological mechanism of inflammation as a causation for fatigue, iv) fatigue as a consequence of disease impact, and v) psychosocial predictors of fatigue.

1.3 Fatigue Measurement

In relation to the topic of measurement, publications to date include a comparative study of the performance of single item visual analogue scales and longer fatigue scales, a systematic review of fatigue scales used to measure fatigue in rheumatoid arthritis (Wolfe 2004; Hewlett *et al.* 2007; Repping-Wuts *et al.* 2009a) and, examination of the validity of single item fatigue scales (Minnock *et al.* 2009; Minnock *et al.* 2010) and of generic multidimensional scales in the measurement of fatigue in patients with rheumatoid arthritis (Repping-Wuts *et al.* 2007; van Hoogmoed *et al.* 2010), and psoriatic arthritis (Chandran *et al.* 2007). More recently, qualitative measures have been used to develop new quantitative tools for measuring fatigue in patients with rheumatoid arthritis: validation studies are ongoing for these newer scales (Nicklin *et al.* 2009; Nicklin *et al.* 2010a; Nicklin *et al.* 2010b).

1.4 Predictors of Fatigue

Early literature on identified predictors of fatigue such as gender, disease duration and inflammation remains conflicting (Belza *et al.* 1993; Belza 1995; Huyser *et al.* 1998; Riemsma *et al.* 1998; Pollard *et al.* 2006). Most of these were cross-sectional studies without an intervention, therefore, causation could not be presumed or confirmed. Studies which have shown a relationship between improvements in fatigue levels and markers of inflammation, following treatment with traditional disease modifying medications as well as newer biologics disease modifying treatments, include randomised controlled trials (Weinblatt *et al.* 2003; Strand *et al.* 2005), and longitudinal observational studies (Pollard

et al. 2006; Heiberg 2010). These findings would suggest that inflammation is a causal factor for fatigue. While observational studies have shown this relationship to be weak and non-significant (Belza 1995; Huyser *et al.* 1998; Riemsma *et al.* 1998; Bergman *et al.* 2009) study designs vary; moreover, participants' disease characteristics, disease states, and treatment regimens lack homogeneity, either pre-dating or excluding patients requiring biologic therapy (Bergman *et al.* 2009).

Studies on the interrelationship between fatigue and disease related symptoms examined many outcomes including greater pain, compromised functional ability, and sleep disturbance; all have been shown to be related to the symptom of fatigue (Belza *et al.* 1993; Belza 1995; Stone *et al.* 1997; Fifield *et al.* 1998; Huyser *et al.* 1998; Riemsma *et al.* 1998; Minnock and Bresnihan 2004; Mancuso *et al.* 2006; Pollard *et al.* 2006). Longitudinal cohort studies in patients with rheumatoid arthritis have demonstrated the interrelationship between fatigue and psychosocial variables such as depressive mood, problematic social support and low arthritis self-efficacy (Tack 1990b; Fifield *et al.* 1998; Huyser *et al.* 1998; Brekke *et al.* 2001; Jump *et al.* 2004; Mancuso *et al.* 2006; Pollard *et al.* 2006).

Over the last decade, spurred by the patient perspective movement, studies seeking further clarification of the nature of the interrelationship between fatigue and other outcomes of the disease process and on the evaluation of the consequences of fatigue in rheumatoid arthritis have been published (Hewlett *et al.* 2005b; Pollard *et al.* 2006; Repping-Wuts *et al.* 2008a; Repping-Wuts *et al.* 2008b; Treharne *et al.* 2008; Repping-Wuts *et al.* 2009a; Repping-Wuts *et al.* 2009c; van Hoogmoed *et al.* 2010). While it is recognised by professionals that fatigue is a very important patient reported symptom in inflammatory arthritis from the patients' perspective fatigue remains unmanageable and professional support remains rare (Repping-Wuts *et al.* 2008b). Further studies are needed on i) the standardisation of approach to measurement, ii) insight and understanding of the interrelationship between the mechanism of inflammation, disease status and the fatigue response, and iii) the appropriate clinical management of this patient reported disease outcome and symptom.

1.5 Deficiencies in Studies to Date

Key subject areas of this salient patient reported symptom of inflammatory arthritis, which would benefit from further clarification, include both the authenticity and utility of fatigue as an outcome measure**.** The initial quantification of fatigue will facilitate the ongoing study and evaluation of fatigue. An assessment instrument that is valid, reliable and feasible for use in daily clinical practice and clinical trials is required to support comparative analysis of all studies and interventions (Repping-Wuts *et al.* 2009c). An agreement on validated assessment instruments for fatigue in both rheumatoid arthritis and psoriatic arthritis is needed to permit comparative analysis across studies. If the rational development of therapeutic interventions for this salient symptom is to happen then firstly it is imperative that this symptom is measured or assessed appropriately as part of routine clinical practice. The correspondence between one-dimension and multi-dimensional instruments needs to be established as the former are probably more feasible for use in daily clinical practice and the latter have a role to play in the more detailed assessment of simple and complex interventions. Further evidence on the validity, reliability, sensitivity and feasibility of both scale types is required in order to standardise the approach to the assessment of fatigue in patients with inflammatory arthritis.

Further clarification on the contributory factors and predictors of fatigue in inflammatory arthritis is required from longitudinal, prospective studies. The relationship between fatigue and the recognised disease characteristics of inflammation such as swollen joints, tender joints, pain, global health, functional ability, and the haematological and biochemical measurements of inflammation- the acute-phase reactants, require further elucidation. Collectively these are known as the core set variables. To date most studies on the relationship between the core outcome measures and fatigue have been cross-sectional observational studies. Therefore, there is a need to examine the relationship between the core outcome measures and fatigue in a prospective, longitudinal, study following treatment interventions for active disease. There is evidence to suggest that the core set variables do not fully explain the variation in the fatigue variable (Pollard *et al.* 2006), this is an aspect which required further exploration so that contributory factors to the unexplained elements of fatigue might be further clarified. Longitudinal cohort studies will

provide further insight into the underlying mechanism of fatigue in patients with inflammatory arthritis.

There is also scarcity of information on the nature of persistent fatigue in patients treated with modern pharmacological biologic therapies. A comparative, prospective study of patients with a poor fatigue outcome versus a cohort with a good fatigue outcome, following treatment of an active disease state, is required to address the dearth of knowledge in this regard.

The nature of fatigue is still regarded as being poorly understood both by those with the disease, and by professionals caring for them. Therefore, it is appropriate that further exploratory study be undertaken on this symptom. Qualitative research helps us to make sense of reality, and to describe and explain the phenomenon of interest. It is appropriate to conduct an exploratory study when little is known about the overall nature of an area of interest and when further insight into quantitative results is required. Elucidation of unique elements of persistent post-treatment fatigue and identification from patients' experiences possible contributory, and potential modifiable, factors to inform practice and improve fatigue outcome are suitable subjects for qualitative inquiry.

1.6 The Importance of this Study

Fatigue is important as an outcome measure in inflammatory rheumatic diseases because those with the disease have identified it as a most important symptom for which a therapeutic intervention is seldom advised or available (Tack 1990a; Hewlett *et al.* 2005b; Repping-Wuts *et al.* 2008a; Repping-Wuts *et al.* 2008b). Moreover, there is agreement between patients, clinicians and researchers that fatigue assessment will aid understanding and, consequently, treatment and management of this symptom of inflammatory arthritis (Gladman *et al.* 2007b; Kirwan *et al.* 2007; Aletaha *et al.* 2008). There is a need for further study on the standardisation of assessment of fatigue and rational development of appropriate therapeutic interventions to treat and promote self-care and professional management of this salient symptom. However, until the contributory factors to fatigue and the elements of unexplained variance of persistent post-treatment fatigue are known, we

will be unable to develop appropriate methods of care. This study addresses both these issues.

1.7 Research Purpose Statement

The purpose of this study on fatigue in inflammatory arthritis in the first instance is to elucidate the clinical characteristics of, and contributory factors to, fatigue in patients with inflammatory rheumatic diseases and, secondly, to explore patients' perceptions and experiences of fatigue and in so doing provide a basis for effective interventions. The type of design most suitable to this study is a mixed methods sequential explanatory design. The mixed methods sequential explanatory design consists of two phases of study: a larger and more dominant quantitative phase followed by a less dominant, supplemental qualitative phase (Morse 2003; Creswell and Plano Clark 2007). The research purpose will be fulfilled according to the following design. The quantitative data will be first collected through a series of clinical assessments and completion of patient reported outcome measures; preliminary data analyses will be undertaken. Subsequently, the qualitative data will be collected through semi-structured interviews. Analyses will be undertaken to help explain, or further elaborate on, the quantitative findings of the initial phase of the study. This second qualitative phase will build on the quantitative phase and both phases will be connected during the intermediate phase and at integration of findings. The logic of this approach is that the findings from the preliminary analysis of the quantitative data will help to identify participants for the qualitative phase of study. Exploration of the patients' perception on fatigue and analysis of these qualitative data will contribute to the further explanation and refinement of the numeric results from the first phase of study. Findings from both phases will be integrated in the presentation and discussion of study results and findings (Morse 2003; Creswell and Plano Clark 2007; Creswell 2009).

The rationale for using a mixed method approach to enquiry was founded in the research problem. The clinical researchers, the scientists and methodologists, and those with the lived experience, the patients, had agreed a research agenda which included standardisation and validation of measurement instruments and exploration of the subjective experience of fatigue (Kirwan *et al.* 2003). Satisfactory answers to both of these problems can only be

acquired by mixing the objective, numeric associations and trends from the quantitative data with the subjective, narrative detail from the qualitative methods of inquiry to provide better understanding of the research issues in their entirety (Tashakkori and Teddlie 1998; Morse 2003; Creswell 2009).

The intent of this two-phase, sequential mixed methods study is to elucidate the clinical characteristics of, and contributory factors to, fatigue in patients with inflammatory rheumatic diseases, namely rheumatoid arthritis and psoriatic arthritis. In the first phase, quantitative research questions will describe and examine the inter-relationship between the independent variables, namely the core set of clinical outcome measures, and mediating variables, such as, pain, sleep and psychosocial variables, and elements of the dependent variable, fatigue. Study participants will be recruited from the researchers clinical work site, a major academic healthcare institution, in Dublin, Ireland. Information gathered from the first phase will be utilised to identify potential participants for the second qualitative phase. In this second phase qualitative interviews will be undertaken with a volunteer group of participants at the same site, to explore patients' perceptions and experiences of persistent fatigue and to help identify a basis for effective interventions.

1.8 Research Purpose

This research purpose is to determine the clinical characteristics of, contributory factors to, and unexplained elements of fatigue in patients with inflammatory arthritis from both the clinical and patient perspective, and in so doing provide a basis for effective interventions.

1.9 Research Objectives

This research purpose will be addressed through the following five objectives which aim: -

I. To quantify levels of fatigue in patients with two different inflammatory rheumatic diseases.
II. To compare the properties of one-dimensional and multidimensional fatigue scales.
III. To define the clinical characteristics of and the relationships between fatigue and the conventional core set of outcome measures.
IV. To elucidate the elements of fatigue not explained by the core set outcome measures.
V. To identify, from the literature and from patients' experiences, potential modifiable factors to improve fatigue outcome.

1.10 Research Phases

Phase 1: Quantitative

Longitudinal, prospective, descriptive study designed to fulfill objectives I-III

Comparative, prospective study designed to address objective IV

Phase 2: Qualitative

Qualitative research methodology designed to explore objectives IV and V

Chapter 2 Research Paradigm: Ways of Thinking, Knowing, Valuing

2.1 Introduction

This chapter provides an overview of the factors which influenced the research design of this project in determining contributing factors and patients' perceptions of fatigue in inflammatory arthritis. In so doing it details the structure of the research process (Blaikie 2009; Creswell 2009). The study design incorporates three key elements-: 1) the research paradigm which refers to underlying philosophical worldviews, assumptions or belief systems, 2) the research strategy or logic of inquiry, which details the types of quantitative, qualitative or mixed methods designs that directed the study and 3) the specific research methods of data collection, analysis and interpretation (Creswell 1998; Tashakkori and Teddlie 1998, 2003a; Bryman 2004).

This specific research strategy outlines the general orientation of the conduct of this proposed study; employing either quantitative-deductive logic where previous knowledge or theory guided research (the causal pathway of fatigue is related to the autoimmune inflammatory response), or qualitative-inductive logic where new constructs or theory were the outcome of research (fatigue makes a unique contribution to outcome assessment) (Morse and Field 1996; Bryman 2004; Blaikie 2009). Ordinarily, quantitative and qualitative research strategies are distinguished by two separate components. Firstly, by their underlying philosophical assumptions (research paradigm) and, secondly, by the distinct methods or procedure employed in conducting the research (Creswell 2009). The research paradigm and research strategy suitable for this study inquiry into fatigue in inflammatory arthritis will now be elaborated.

2.2 Introduction to Philosophy

The role of philosophy in the study of the phenomenon of fatigue in inflammatory arthritis is best explained through a brief historical overview of the interconnectedness between philosophy, and health and social science research. Philosophers and the discipline of philosophy are essentially about contributing to knowledge and understanding (Sinclair 2008). Philosophical assumptions behind health and social science research represent ways of thinking, knowing and valuing. In conducting this health research these assumptions helped to ensure the research was structurally sound, trustworthy, and served to answer the question posed (Greene and Caracelli 2003; Filmer *et al.* 2004). Indeed the term 'scientist' was coined in 1833, in part, to distinguish the more practical "cataloguers and experimenters" from the 'aloof philosophers" (Sinclair 2008). Consequently, scientific research within the social and health sciences as we know it today is guided by different philosophical perspectives or research paradigms. These include the so called opposing schools of postpositivism and constructivism, and pragmatism (Bryman 2004; Blaikie 2009; Creswell 2009). The fundamental differences between these philosophies are centred on the two opposing schools of thought; these are outlined as a trilogy of assigned truths or concepts from the philosophy of knowledge, branches of the core subjects of philosophical study (Morgan 2007). This trilogy includes issues related to epistemology, ontology and axiology which are collectively referred to as metaphysical questions; higher order assumptions related to the nature of reality and truth (Morgan 2007). In relation to this study and in everyday language, these were ways of thinking, knowing, and valuing the knowledge acquired in and from this research practice, and will be further explained.

2.3 Metaphysical Questions and Fatigue in Inflammatory Arthritis

Epistemology (what is knowledge-and the credibility and legitimacy of how we know what we know), challenges the researcher on the suitability of the natural science model of research in the study of the social world and the world of health care, such as the phenomenon of fatigue in inflammatory arthritis (Morgan 2007). Ontology (the nature of existence, being, or reality; what kinds of things exist?), questions whether the social world

is external to, or constantly being fashioned by people. The 'people' in this study are referred to as the researcher, and key stakeholders, chiefly those reporting the symptom of fatigue, and their professional carers. Ontology asks is fatigue what the researcher and professionals measure or quantify it to be, or is it what those who experience the symptom say it is? Axiology (the place of values in research, including ethics and aesthetics) relates to the influence of practical issues, such as the researchers' personal values, had on the study process (Tashakkori and Teddlie 1998, 2003a), and how these might have influenced the conduct of study of a subjective symptom like fatigue. In this study these metaphysical questions influenced the choice of research strategy and methods (the process of research) and the underlying paradigm of pragmatism. The ways of thinking, knowing and valuing translated into the distinctions drawn between quantitative and qualitative research strategies (Greene and Caracelli 2003), and the use of both of these approaches to answer the research questions on the phenomenon of fatigue in patients with inflammatory arthritis. The appropriateness of pragmatism as the paradigm of choice is next explained.

2.4 Pragmatism the Paradigm of Choice: Rationale

Pragmatism is presented as the appropriate research paradigm for this study. The rational/ arguments advanced in support of pragmatism concentrates on the following: - i) compatibility thesis or support for mixed methodology, in order to address the research purpose, ii) the variety of the five research objectives posed, iii) the logic of inquiries required to find confirmatory answers and further questions, iv) the contention that truth is what works to find the answers at the time, and finally v) the dialectic stance or tensions between different approaches (Greene and Caracelli 2003), to the quest for truth about the symptom fatigue.

2.5 Compatibility Thesis

Pragmatists advocate the compatibility thesis; they consider 'truth' to be 'what works', and focus on finding solutions to research problems or questions. The pragmatic focus is more on the research problem of interest than on methods and advocates the use of all approaches

available to help understand the problem (Patton 2004). They use both quantitative and qualitative data as a means to acquire the best understanding of the research problem (Creswell 2009). The major pragmatic principle is that quantitative and qualitative methods are compatible (Howe 1988). The roots of pragmatism were traced to its American founding fathers, Pierce, James and Dewey, and more recently to the scholars Quine, Rorty and Davidson (Murphy and Rorty 1990; Cherryholmes 1992). More recent writings highlight the similarities in the fundamental values between qualitative and quantitative research strategies (Reichardt and Rallis 1994). Recognising that both quantitative and qualitative methods have many benefits and limitations, researchers are encouraged to combine insight and procedures from both approaches to produce a superior method (Burke Johnson and Onwuegbuzie 2004). Pragmatism supports the researcher to embrace empirical phenomena and to adopt a commonsense practical thinking perspective or lens (Maxcy 2003). Pragmatism, in this study directed the researchers attentions to the methodological more than the metaphysical concerns (Morgan 2007). Moreover, the pragmatic research paradigm supports the use of a mixed methods research strategy (Tashakkori and Teddlie 1998, 2003a), appropriate to this study's purpose.

2.6 Variety of Objectives

The rationale for the choice of the philosophical perspectives of pragmatism to guide this study was influenced by the recommendation that when a research project includes a variety of objectives more than one research strategy may be required to answer them (Blaikie 2009). The pragmatic research paradigm supports the use of a mixed methods research strategy in health research (Tashakkori and Teddlie 1998, 2003a). The overarching goal of this study on fatigue in patients with inflammatory arthritis was to aid understanding of this patient reported symptom, and the identification of appropriate therapeutic interventions to improve its management. Multiple perspectives (objective /confirmatory and subjective/exploratory) were required to answer the study objectives and the nature of these respective concepts influenced the researcher's field decisions (Greene and Caracelli 2003). Examination of the study objectives highlights their diverse nature: i) quantification of levels of fatigue, ii) comparison of measurement properties of fatigue scales, iii) defining the clinical characteristics of and the relationships between fatigue and

the conventional clinical core outcome measures, iv) clarifying unexplained elements of fatigue and lastly, v) the exploration of patients' perceptions, experiences and meaning of this phenomenon for all key stakeholders. The first four required a confirmatory answer while the latter required further exploration.

The first three objectives were deductive in nature, working from the theory that fatigue (dependent variable) is a consequence of the autoimmune inflammatory response, and so explained by the 'core set' of clinical outcome measures (the independent variables). The main deductive theoretical drive of this study was to either prove or disprove this hypothesised relationship, working from cause to effect within a post positivistic framework using a deductive logic. Quantitative purists (positivists and post-positivists) contended that social science inquiry should be objective, yield generalisations which remain independent of time and context, where the researcher remains emotionally unattached, unbiased and uninvolved with the object of study while testing a stated theory or hypothesis. However, the theoretical drive of the study then shifted from objective deductive to an inductive study of the concept of fatigue to help further explore and find meaning of this phenomenon in inflammatory arthritis. The study purposely explored the uniqueness or unexplained aspects of fatigue guided by the pragmatic beliefs in the 'theory ladenness' of facts, meaning that the research is influenced by the theory or hypothesis of the researcher, and belief in the 'fallibility of knowledge', and 'under verification of theory by fact' (Tashakkori and Teddlie 1998, p. 13) that all theories cannot be proven or fully explained. For example, pragmatism acknowledges causal linkages, such as the relationship between fatigue and joint inflammation. Moreover, it also acknowledges that such relationships cannot be pinned down and definitively explained by one theory. Because knowledge is fallible, pragmatism embraces more than one explanatory 'fact' or point of view about fatigue recognising the influences exerted by both the researcher and the participants in this regard. Pragmatism argues against dominant systematic philosophies and their grand either-or beliefs in relation to ways of thinking, knowing and valuing (Nielsen 1991).

2.7 Logic Theory

Logic theory, in philosophical terms, refers to the validity of an argument or laws of thought (Sinclair 2008); in this research context it refers to the validity of an argument in explaining or predicting the study findings. Hypotheses are deduced from theory and subjected to empirical scrutiny. In this study, the first three objectives were designed to use deductive logic to test the hypothesis that fatigue is not fully explained by the inflammatory process; deducing rationalises the explanation given. While the fourth and fifth objectives used inductive logic primarily; this suggests a tentative hypothesis or an explanation of the phenomenon of fatigue as we see it. This research question used both deductive and inductive logic; the fourth objective moved between both deductive and inductive logic and reasoning to determine and quantify the unique contribution made by fatigue to assessment of outcome, and to explore unique elements of fatigue from the patients' perspective. In so doing it moves between theory and research, which serves as a means to discover new and still unknown and unexplained concepts; this process of inference to the best explanation is termed abductive reasoning (Erzberger and Kelle 2003; Blaikie 2009).

2.8 Truth: What Works

Truth is what works, and it is not contingent on either of the philosophical dualisms such as reality being either independent of the mind or within the mind (Creswell 2009). Drawing from the core philosophical assumptions, a reality perspective of the phenomenon of fatigue was best achieved by looking beyond cause and effect (the body) to explore who, what, where, when and how, influences this phenomenon of interest (the mind). Such a model of inquiry was best served in this study through a pragmatic theoretical perspective. The overarching purpose of the pragmatic research paradigm was to provide a theoretical lens through which our ways of thinking, knowing and valuing of this study's findings will serve to enhance our understanding of the phenomenon of fatigue in inflammatory arthritis. The qualitative protagonists (constructivists/intrepretivists) contend that multiple–constructed realities exist in relation to the experience of fatigue by patients, that time and context free generalisations therefore neither exist nor are desirable, that research is value-

bound as it is influenced by the interrelationship between the patients and the researcher, cause and effect cannot be differentiated and objectivity is impossible as the subjective 'knower' (the patient) is the only source of the reality of the symptom fatigue. The contention of quantitative purists (positivists and post-positivists) would be that research inquiry into fatigue should be measurable and quantifiable on a fatigue scale (objective), findings would be reproducible and capable of being generalised to other groups of patients (yield time and context free generalisations), that the researcher should remain emotionally unattached to the participants and the symptom, (unbiased and uninvolved with the object of study), while testing a stated theory or hypothesis, and exploring cause and effect (deduction). The incompatibility debate puts forward that quantitative and qualitative research paradigms and, moreover, their associated methods of inquiry cannot and should not be mixed (Sandelowski 2000a; Burke Johnson and Onwuegbuzie 2004). However, this paradigm debate has evolved through the stages of positivism, post-positivism, constructivism, and the paradigm war through to pragmatism and the compatibility thesis, that is, fulfilling the research purpose and objectives (Tashakkori and Teddlie 1998, 2003a).

The philosophy of pragmatism, proposed as the third paradigm, is capable of bridging the gap between quantitative and qualitative positions (Burke Johnson and Onwuegbuzie 2004). For this study it provided a framework to address the study purpose using both deductive and inductive logic through mixing methods of inquiry. With respect to the objectives the main theoretical drive was deductive with a supplemental qualitative component. This supported the researcher to answer the questions posed in a structurally sound, robust and honest manner with respect to the perspectives of all key stakeholders (Filmer *et al.* 2004); the clinicians and the patients.

2.9 Dialectic Stance

Pragmatism offers a dialectic viewpoint; it supports conflicting philosophical tensions between respective quantitative and qualitative purists about the purpose of science in society and, moreover, a process of reaching a better understanding of human phenomena (Greene and Caracelli 2003). This broad approach was chosen to serve the interest of, and even the tension between, two key stakeholder groups. These two groups were the clinical

research scientists and methodologists, largely from the positivistic school of outcomes research, focused on 'truth, discrimination and feasibility' (Boers *et al.* 1998), and patients who nominated fatigue as an important outcome (Kirwan and Hewlett 2007), experiencing the symptom or phenomenon of interest within the subjective, theory laden world of multiple constructed realities (Tashakkori and Teddlie 1998; Carr *et al.* 2003; Greene and Caracelli 2003; Kirwan *et al.* 2005a). The different philosophical assumptions: multiple constructed realities; theory-ladenness of facts and value-ladenness of inquiry, meaning that research is influenced by the theory or hypothesis, and values of the researcher, respectively; underdetermination of theory by fact; belief in the fallibility of knowledge; abductive research cycle; all serve to offer different and even contradictory or opposing ideas and perspectives (Tashakkori and Teddlie 1998). Pragmatism, as a philosophy, recognises the value of these differences in their potential to generate a more meaningful and better understanding of the phenomenon of interest, through mixing strategies of inquiry.

2.10 Pragmatism and a Mixed Methods Strategy

Philosophically, mixed methods make use of the characteristics of pragmatism. The logic of inquiry combines induction (discovery of patterns, arguing from the particular to the general, positing relationships), deduction (inferring from what has preceded, testing of theories and hypotheses, arguing from general to the particular) and abduction (uncovering and relying on the best set of explanations for understanding findings) (Erzberger and Kelle 2003). As a strategy of inquiry, mixing methods is regarded as inclusive, pluralistic, and complementary, permitting researchers to follow research questions in a way that offers the best chance of obtaining useful answers (Burke Johnson and Onwuegbuzie 2004). The combination of factors which influenced the choice of mixed methods included the characteristics of the research objectives and the respective merits of the individual strategies of inquiry required to fulfill these objectives. Other influencing factors included the researcher's personal research experience in the area of outcome research and previous collaborative work with the audience of interest, that is patients, clinicians and researchers in the area of outcome research (Kirwan *et al.* 2003).

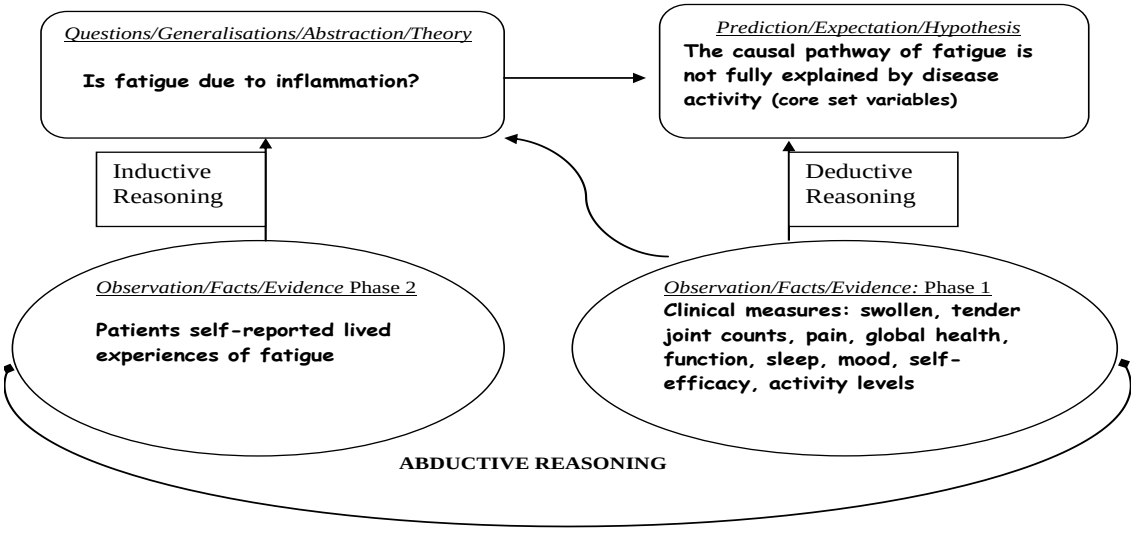
2.11 Characteristics of the Research Question

The decision to undertake mixed methods research was primarily based on the fact that the phenomenon of interest, fatigue, an outcome in inflammatory arthritis, was identified by those with the disease as a salient symptom for which management is seldom advised or available (Tack 1990a; Wolfe *et al.* 1996; Wells *et al.* 2003b; Kirwan *et al.* 2005b; Davis *et al.* 2007; Repping-Wuts *et al.* 2008a; Repping-Wuts *et al.* 2008b). The clinical researchers, and those with the lived experience, the patients, previously agreed a research agenda, which included standardisation and validation of measurement instruments and exploration of the subjective experience of fatigue (Kirwan *et al.* 2003). Satisfactory answers to both of these problems can only be acquired by mixing quantitative and qualitative methods of inquiry to provide better understanding of the research problem (Tashakkori and Teddlie 1998; Creswell 2009). Questions related to outcome measurement originate from the medical field of outcome research where quantitative methodology dominates. A quantitative approach was required as the research question sought to identify factors that influence the outcome variable fatigue, and gain understanding of the best predictors of outcome (independent variables) (Kirwan *et al.* 2003; Kirwan *et al.* 2005b; Kirwan and Hewlett 2007; Creswell 2009). The validation and comparison of the measurement properties of questionnaires is also a psychometric activity requiring recognised statistical procedures based on numeric data (Oppenheim 1992; Trochim 2006).

2.12 Characteristics of the Methods of Inquiry

On the other hand, exploration of the concept of fatigue requires inquiry into patients' perceptions and meaning of this poorly understood phenomenon using qualitative approaches (Tashakkori and Teddlie 1998; Bryman 2004; Hanson *et al.* 2005; Tashakkori and Creswell 2007; Repping-Wuts *et al.* 2008a; Creswell 2009; Doyle *et al.* 2009). The orientations of the respective methods coupled with the current status of the phenomenon of fatigue in outcome research exerted an influence in the choice of research design (Greene *et al.* 1989).

Figure 2-1: The research cycle



As depicted in Figure 2-1 this research project started from the premise or generalisation that fatigue in inflammatory arthritis is a consequence of the chronic inflammatory process and systemic manifestations of this immune driven inflammatory disease. This question or generalisation, drawn from previous research, was examined deductively by testing this hypothesised relationship, and by prediction of outcome. Using qualitative methods of inquiry, facts and observation were also gathered directly from patients, to further explore the who, what, where, and why of their experiences of living with fatigue (Neergaard *et al.* 2009), and inference made through inductive reasoning. The study moved between both types of reasoning typical of abductive logic, (uncovering the best set of explanations for understanding findings), within a pragmatic paradigm (Tashakkori and Teddlie 1998; Miller and Brewer 2003) (Figure 2-1).

2.13 Pragmatic Purpose of Mixing Methods

The overarching purpose of mixing methods of inquiry was to address the research purpose and different objectives of the study (Bryman 2004; Doyle *et al.* 2009). However, mixing

methods of inquiry served more than one purpose in this study. It served to validate results and findings on whether fatigue is always due to disease activity (triangulation), integrating the numeric and narrative data in the discussion of the results disclosed contradictions and fresh perspectives (initiation) especially with regard to the relationship between fatigue and other patient reported outcomes. Mixing methods permitted more developed explanation of findings (development) in the discussion of results in an attempt to elucidate unique elements of fatigue. The exploration of patients' experiences of, and self-management strategies for, fatigue added a dimension of completeness to a study on a poorly understood concept and undermanaged symptom of inflammatory arthritis (complementarity). Finally, the narrative integration of both sets of data added breadth and scope to this study and consequently to the explanation of the study results (development) (Greene and Caracelli 2003; Tashakkori and Teddlie 2003b).

2.14 Conclusion

As stated the purpose of this study was to determine the clinical characteristics and contributing factors to, and patients' perceptions of, fatigue in inflammatory arthritis: and make a meaningful contribution to the limited body of knowledge on fatigue in inflammatory arthritis. The choice of research paradigm (worldview or theoretical lens), and research strategy focused on the compatibility of quantitative and qualitative methodology in providing answers to different questions at different stages of the study. Based on the pragmatic premise that 'truth is what works' (Howe 1988) the approaches chosen were those most conducive to providing answers to the research questions (Tashakkori and Teddlie 1998). These ranged from the postpositive quantitative origins of the question within the context of outcome measurements to the more qualitative meaning of the experience of fatigue constructed from the perspective of those with the disease and symptom. Mixed methodology was chosen because it provided a research strategy that worked for the purpose of providing answers to questions, albeit from different origins (researchers and patients), on a salient topic of mutual interest: the measurement, mechanisms, meaning and management of fatigue in inflammatory arthritis. The steps taken in designing this study included the traditional steps of establishing a research purpose, research objectives and type of data to collect. Additional consideration was given

to deciding on the use of pragmatism as the theoretical lens (Tashakkori and Teddlie 1998; Greene and Caracelli 2003; Morgan 2007; Creswell 2009).

The pragmatic theoretical lens presented in this chapter was the appropriate paradigm for this study, using abductive logic to uncover the best set of explanations to understand the findings. Tenets of postpositivism and constructivism were respected appropriately through the research cycle. Deductive and inductive reasoning were employed within the separate phases. The specific research methodology and method of data collection used to conduct this study are discussed in detail in Chapter 4.

Chapter 3 LITERATURE REVIEW

3.1 Research Justification: Introduction

The purpose of this chapter is to introduce the problem of fatigue in inflammatory arthritis as currently described in the literature. This review of relevant literature provides the reader with a framework which demonstrates the importance of the proposed study, and facilitates the comparison of its findings with results of previous studies in the area. The literature is presented in a format that firstly orientates the reader to the broad subject area of autoimmune rheumatic diseases and current management strategies. The main focus, however, is on the presentation of broad themes from the literature on fatigue in inflammatory arthritis, using an integrative approach (Cooper 1989). This serves to frame the problem of fatigue in inflammatory arthritis and to provide a justification for the study undertaken. These respective sections of the literature are presented as follows:-

A biomedical perspective on inflammatory arthritis

This includes background in the form of a brief classification of the rheumatic/ musculoskeletal disorders, followed by an overview of the autoimmune process, the pathogenesis of, the contributory factors to, and the clinical characteristics of inflammatory arthritis. An overview of the management of early inflammatory arthritis, including modern pharmacological approaches to treatment and the aim of modern drug therapies is provided.

Outcome measurement

This includes patient reported outcomes, for the purpose of monitoring the course of the respective conditions of rheumatoid arthritis and psoriatic arthritis. These are presented in detail as evaluation of patient outcome is central to the topic of interest.

Patients' perspectives and the salient symptomatic experience of fatigue in inflammatory arthritis

This reviews characteristics related to meaning, prevalence, and contributory factors to, and the multidimensional nature of, fatigue from available literature.

3.2 Biomedical Perspective of Rheumatoid Arthritis and Psoriatic Arthritis

3.2.1 Rheumatic diseases and inflammatory arthritis

The World Health Organisation classifies the disorders of the musculoskeletal system into five main groups: back pain, periarticular conditions also known as soft tissue or regional disorders, bone diseases, osteoarthritis and inflammatory arthritis (Woolf and Pfleger 2003). The word arthritis comes from the Greek 'arthron' which means 'joint', and 'itis' meaning 'inflammation'; plural: arthritides. Inflammatory arthritides are chronic and progressive autoimmune conditions that cause persistent joint inflammation and joint destruction as well as producing systemic symptoms (Emery *et al.* 2008). The estimated overall prevalence of the inflammatory arthropathies is approximately 2% of the population; Table 3-1 represents the estimated prevalence of the more usual inflammatory diseases listed in Klippel and Dieppe (1997).

Table 3-1: Estimated prevalence for inflammatory arthropathies

Disorder	Prevalence (%)
Rheumatoid arthritis	1.0
Crystal arthropathies	1.0
Ankylosing spondylitis	0.1
Psoriatic arthritis	0.1
Juvenile idiopathic arthritis	0.06
Systemic lupus erythematous	0.02

National population samples are unavailable for most specific rheumatic conditions, estimates are mostly derived from published studies of smaller, defined populations (Power *et al.* 1999; Helmick *et al.* 2008).

The separate disease entities of rheumatoid arthritis and psoriatic arthritis are the inflammatory arthritides of interest in this study of fatigue. An overview of the autoimmune pathogenesis, epidemiology, clinical manifestations, and management will be presented in advance of reviewing this main subject area of interest.

3.3 Inflammatory Arthritis: Pathogenesis

The origins and effects of the inflammatory arthritides is an autoimmune response, which is described as a sustained specific immune response against self-antigens (auto-antigens) (Panayi 1993; Schulze-Koops and Kalden 2003). It is recognised that the mechanisms which lead to the destruction of tissue, and the associated impairment or loss of joint and organ function during the course of these autoimmune arthritides, are essentially the same as the protective immune response against invasive microorganisms (Schulze-Koops and Kalden 2003).

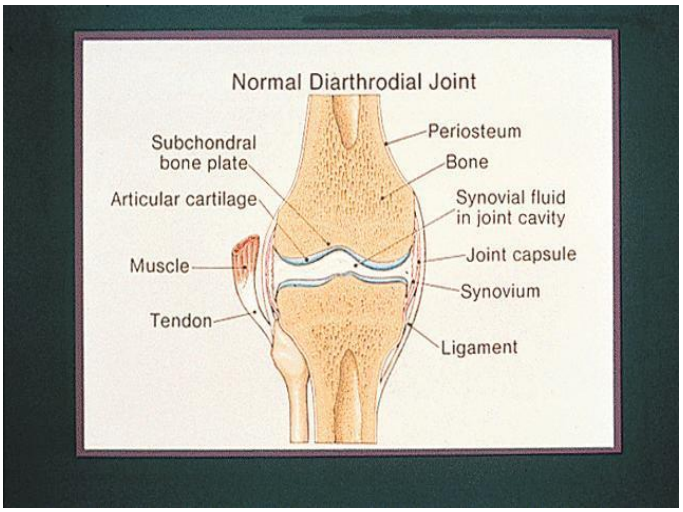
3.3.1 The immune response

Components of the immune system include innate immunity, and the specific immune response. Both innate and specific immunity depend on the ability of the immune system to distinguish between ‘self’ and ‘non-self’ or invader molecules. These non-self molecules are known as antigens, short for antibody generators (Alberts *et al.* 2002). Inflammation is part of the immune system’s normal response to antigenic triggers such as infection and injury. The dynamic response triggered is a cascade of physiological changes that leads to the cardinal signs of inflammation; rubor (red), calor (hot), dolor (painful), and tumour (swelling) (Tortora and Derrrickson 2006). In all autoimmune diseases, the affected individual displays an inability to distinguish foreign molecules from some of the body's own molecules. In inflammatory arthritis this results in a targeted response against synovial tissue that lines all diarthrodial (freely moveable) joints (Figure 3-1). This causes a

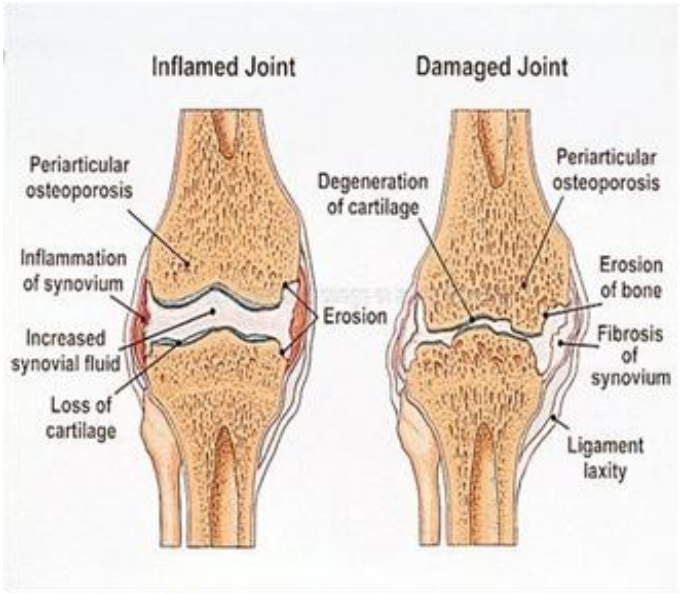
‘synovitis’, which is inflammation of the synovial membrane which lines the cavity of all diarthrodial joints (Pincus and Callahan 1989; Bresnihan 2004). The resultant arthritis is due to persistent synovitis of the affected joints; the main disease expression is in body compartments which are surrounded by a synovial lining layer. Such compartments include the freely moveable synovial joints (Lem van Lent and van den Berg 2003).

Synovitis results in joints becoming red, swollen, tender, warm and painful, joint function is restricted by the associated symptoms of pain and stiffness. If left untreated, the protracted synovitis leads to joint destruction which is responsible for the deformity and disability associated with the inflammatory arthritides (Bresnihan 2004) (Figure 3-1).

Figure 3-1: Normal diarthrodial joint and rheumatoid arthritis affected joint



In a typical diarthrodial joint the articular surfaces are covered by a smooth layer of hyaline cartilage and enclosed in a fibrous capsule. The fibrous capsule merges externally with periostium, tendons, ligaments and fascia and internally it merges with the synovial membrane. The synovial membrane lines the joint cavity and the surfaces of the bone not covered by hyaline cartilage. A small amount of synovial fluid is usually present within the joint cavity.



In a joint affected by inflammatory arthritis the inflamed synovium proliferates into the joint space invading cartilage, bone and ligaments leading to joint damage and deformity (Bresnihan 1999; Veale *et al.* 2005). With persistent inflammation, there is increased circulation through the joint, and the bone adjacent to the joint line becomes progressively depleted of its normal mineral make-up. This is referred to as peri-articular or juxta-articular osteoporosis (ACR 2010).

Images reproduced by kind permission of American College of Rheumatology Image Bank (American College of Rheumatology 2010) (Appendix 1).

3.3.2 Cellular infiltration

Cells of the innate immune system which infiltrate the synovium include monocytes, (Lem van Lent and van den Berg 2003), neutrophils, fibroblasts (Lee and Firestein 2003), dendritic cells (Thomas *et al.* 2003), and mast cells (Valent and Kiener 2003). Those of the specific adaptive immune response which infiltrate the synovium include both B-lymphocytes, and T-lymphocytes (Davidson *et al.* 2003; Schulze-Koops and Kalden 2003), Clinical trials of targeted B-cell therapies utilised to treat rheumatoid arthritis have been shown to statistically and clinically improve both joint symptoms and the constitutional symptom of fatigue (Cohen *et al.* 2006). In contrast, the function of B lymphocytes is not clear in psoriatic arthritis as this disease entity is not associated with high circulating antibody levels (Veale *et al.* 2005). T-cells, and specifically CD*4+ T cells, have been shown to be of fundamental importance in initiating, controlling and driving both the protective and destructive immune responses. Activated CD4+ T cells are found in inflammatory infiltrates in rheumatoid arthritis and it is recognised that they play a central role in the initiation and perpetuation of the autoimmune tissue-damaging inflammatory response (Schulze-Koops and Kalden 2003). This concept is the basis of many of the T-cell directed therapies used to treat both rheumatoid arthritis (Schulze-Koops and Kalden 2003) and psoriatic arthritis (Veale *et al.* 2005).

*[CD= cluster of differentiation; nomenclature for classification of cell surface markers (Barclay *et al.* 1997)]

3.3.3 Angiogenesis and cytokines

Other factors are at play in this protracted inflammatory response. These include angiogenesis, which is new blood vessel formation (Fearon and Veale 2007), and the role played by cytokines. Cytokines are soluble proteins that act as chemical messengers between antibody mediated and cell mediated immunity (Firestein 1998; Feldmann and Maini 2003). The identified cytokines, interleukin (IL)-1, IL-6, IL-15, IL18 and tumour necrosing factor-alpha (TNFα), are known as pro-inflammatory cytokines. These are not constitutively produced, but are generated during acute inflammation. The normal tightly

regulated balance between pro-inflammatory cytokines and anti-inflammatory cytokines is lost in inflammatory arthritis; pro-inflammatory cytokines becoming chronically increased leading to prolonged, disproportional inflammation (Feldmann *et al.* 2004). This chronic inflammation of the synovium leads to invasion of the synovial tissue into the adjacent structures; cartilage, matrix and bone. This in turn results in joint destruction, deformity, and disability, and severe morbidity (Firestein 1998; Tak and Bresnihan 2000). Raised levels of these pro-inflammatory cytokines have been demonstrated in the joint fluid of patients with rheumatoid arthritis and early psoriatic arthritis. TNFα has been shown to be a key proinflammatory cytokine which correlates with both disease progression and severity in both skin and joints. Novel medications, known as biologic therapies, target these cytokines in order to reduce the signs and symptoms of inflammatory arthritis and thus strive to achieve clinical remission from the disease process (Emery *et al.* 2008).

3.3.4 Summary of pathogenesis

The precise pathogenesis of inflammatory arthritis remains unclear. The causal hypothesis ordinarily proposed is the action and complex interplay of multiple antigenic triggers, coupled with the presence of a background genetic predisposition to initiate a self-perpetuating series of autoimmune responses in the synovial compartment (Panayi 1993). The continued scientific study of these multiple overlapping mechanisms of disease initiation, and pathways of regulation and perpetuation, provide the basis for the development of novel pharmacological therapies. These novel medications are used to treat both the articular consequences (Firestein 1998; Bresnihan 1999), and systemic clinical manifestations, such as fatigue, of these potentially destructive autoimmune inflammatory arthropathies of rheumatoid arthritis and psoriatic arthritis (Wolfe and Michaud 2004; Cohen *et al.* 2006).

3.4 Contributory Factors to Rheumatoid Arthritis and Psoriatic Arthritis

This next section of the literature review adopts a comparative approach. The separate disease entities of rheumatoid arthritis and psoriatic arthritis are presented concurrently looking at definitions, epidemiology, diagnosis, and clinical manifestations including signs and symptoms.

3.4.1 Definitions

Rheumatoid arthritis is an immune mediated disease process defined as a chronic, progressive, systemic, inflammatory disorder of unknown cause (Matteson *et al.* 1997). It is the most common chronic inflammatory joint disease (Symmons 1995). The most pronounced pathology is in synovial joints, also known as the diarthrodial or freely movable joints (Maini and Feldmann 1998). The majority of patients test positive for the rheumatoid factor auto-antibody on serological testing (sero-positive), rheumatoid factor is non-specific for rheumatoid arthritis and more than 30% of patients test negative (sero-negative), (Emery *et al.* 2008; Brown and Boers 2010). However, constitutional features of rheumatoid arthritis, such as fatigue, sometimes predominate the articular symptoms (Matteson *et al.* 2003).

Psoriatic arthritis is a recognised unique arthropathy broadly defined as a chronic, immune mediated inflammatory arthritis associated with psoriasis and usually negative for rheumatoid factor on serological testing (sero-negative) (Gladman *et al.* 2005a; Helliwell and Taylor 2005; Langley *et al.* 2005). It was this absence of rheumatoid factor on serological testing in the majority of cases that contributed to the recognition of psoriatic arthritis as a separate entity (Jones and McHugh 1994; Gladman *et al.* 2005a).

Synovial joint inflammation, or synovitis, is common in both rheumatoid arthritis and psoriatic arthritis (Barton 2002).

3.5 General Overview

Rheumatoid arthritis is primarily a disease of the synovial joints. There are also extra-articular (outside the joints) manifestations, such as rheumatoid nodules and a variety of systemic or constitutional features (Maini and Feldmann 1998). Rheumatoid arthritis is characterised by the pattern or distribution of the joints involved. At presentation the classic distribution of joint involvement is a symmetrical synovitis of the multiple small joints (polyarthritis) of the hands and feet (Harris 2001), hip and knee joints are also frequently implicated (Maini and Feldmann 1998). Affected joints become red, swollen, hot, and tender on palpation and movement; the associated joint stiffness experienced by patients, a phenomenon referred to as gelling, prevents their use. This prominent feature of increased stiffness upon waking (early morning stiffness) may last for more than an hour (Emery 1999; Matteson *et al.* 2003). The associated extra-articular manifestations and a variety of systemic or constitutional features which also occur (Maini and Feldmann 1998) include fatigue, malaise, and weight loss that may occur early in the disease presentation and sometimes overshadow the joint manifestations. Inflammation can involve other organ systems, including blood vessels, the nervous system, heart and lungs (Matteson *et al.* 2003). Rheumatoid arthritis is associated with increased morbidity and mortality (Pincus and Callahan 1989; Gonzalez *et al.* 2008), a considerable impact on patients' quality of life (Minnock *et al.* 2003a, 2003b; Mau *et al.* 2008), and a high cost to society (Osiri *et al.* 2007; Kobelt and Jonsson 2008).

Psoriatic arthritis is a multisystem disorder which presents with a variety of patterns of skin (cutaneous), axial skeleton and peripheral musculoskeletal manifestations. The burden of these combined disease entities on quality of life has been demonstrated (Gladman *et al.* 2005a). As with rheumatoid arthritis pain, function and fatigue are the patient reported outcomes most frequently prioritised for intervention by those with the disease (Mease *et al.* 2005a). However, a variety of articular and extra-articular clinical features distinguish psoriatic arthritis from rheumatoid arthritis. Specific clinical features include the distribution of affected joints; a distal interphalangeal joint predominant pattern, the degree of erythema over affected joints, the presence of spinal involvement, the presence of enthesitis, (enthesis/entheses are site(s) of tendinous or ligamentous attachments to the bone; enthesitis indicates inflammation at the site, also called

enthesopathy), the nature of joint deformity, and the lower level of tenderness of joints (Gladman 1998). Extra-articular manifestations distinguishing psoriatic arthritis from rheumatoid arthritis include the absence of rheumatoid nodules, the significant lower incidence of rheumatoid factor presence in serum, and the typical clinical feature of dactylitis. Dactylitis is inflammation of an entire digit due to a combination of synovitis and tenosynovitis (Gladman *et al.* 2005a). It is suggested that psoriatic arthritis is primarily a disease of the entheses with secondary synovial inflammation (Barton 2002). Inflammation can involve other organ systems, including the eyes (iritis or uveitis), the urinary system (urethritis), and gastrointestinal mucosa (Gladman 2007). Psoriatic arthritis is associated with an increased mortality related to disease severity (Wong *et al.* 1997). Patients have a reduced quality of life compared with those with psoriasis alone or with healthy controls (Husted *et al.* 1997; Zachariae *et al.* 2002).

Although rheumatoid arthritis and psoriatic arthritis are distinct disease entities the impact of these diseases is reported to be similar in terms of function and overall quality of life (Sokoll and Helliwell 2001).

3.5.1 Epidemiological aspects

Prevalence

The prevalence of rheumatoid arthritis in the adult population, estimated at 0.5-1%, is relatively constant across many populations (Power *et al.* 1999; Simonsson *et al.* 1999; Silman and Pearson 2002). The advised incidence for health planners is that 25–50 people from a population of 100,000 will develop typical rheumatoid arthritis (Uhlig and Kvien 2005). It affects women 2-4 times more frequently than men and the peak age of onset is 30 to 50 years (Ostensen *et al.* 1983; Hannan 1996; Kvien *et al.* 2006). The prevalence of rheumatoid arthritis increases with age (Gordon and Hastings 2004), and gender differences diminish in the older age group (Lawrence *et al.* 1998; Kvien *et al.* 2006). It is hypothesised that this age of onset has risen in recent years (Symmons 2002), and that the incidence and severity has reduced over the past 3-4 decades (Silman 1992). While, a decline in prevalence over the last decade is not supported by recent studies (Englund *et al.*

2010), the observed improvement in health status in patients with rheumatoid arthritis is attributed to access to better and more aggressive treatments (Uhlig *et al.* 2008).

The estimated prevalence of psoriatic arthritis in the general population is approximately 1% (Gladman *et al.* 2005a). The incidence is equal in males and females although the pattern of disease presentation differs. Spinal involvement is more frequent in men, and a rheumatoid arthritis like presentation is more frequently seen in women. Usual age of onset is 30-50 years. The difficulty in estimating the exact prevalence of psoriatic arthritis is attributed to the lack of consensus on classification and diagnostic criteria which in turn contributes to diagnostic difference even between the recognised experts in the field (Gladman *et al.* 2005a; Helliwell and Taylor 2005) .

3.5.2 Genetic factors

Evidence exists of both genetic and environmental contributions, and the interactions between them, to the development of rheumatoid arthritis (Symmons 1995). While descriptive epidemiology suggests a genetic link, in contrast to other autoimmune diseases, such as insulin-dependent diabetes and multiple sclerosis, the familial recurrence risk in rheumatoid arthritis is smaller (Jones *et al.* 1996). Multiple genetic factors are indicated, and a Mendelian inheritance pattern is not demonstrated (Deighton *et al.* 1992). The most definite genetic association with rheumatoid arthritis is the human leucocyte antigen (HLA) alleles of the major histocompatibility complex. More specifically, a predisposition to rheumatoid arthritis and moreover to the severity of the disease expression is linked to the class II histocompatibility antigens, namely, HLA-DR4 (Silman *et al.* 1993; Fries *et al.* 2002; Silman and Pearson 2002). Other genetic factors shown to influence predisposition to rheumatoid arthritis include variations in genes for various proteins such as cytokines, which are heavily implicated in driving the inflammatory process. It is likely therefore that, in addition to HLA, the development of rheumatoid arthritis is linked to several other genetic factors (Silman and Pearson 2002).

Psoriatic arthritis and psoriasis are interrelated disorders, as most patients with psoriatic arthritis also have psoriasis. Epidemiological and immunogenetic studies have

demonstrated that both disorders are highly heritable, and the prevalence of psoriasis is 19 times higher among first degree relatives of an individual with psoriatic arthritis compared with the general population (Rahman and Elder 2005). The tendency for strong familial clustering of psoriatic arthritis was demonstrated in a robust study in 1973 (Moll and Wright 1973a). Strong associations in psoriatic arthritis and psoriasis have been noticed in the genes of the major histocompatibility complex region, in particular, the class 1 HLA. Individual antigens have been shown to be associated with certain disease features. For example, axial skeleton involvement is associated with the HLA-B27 antigen (Elder 2005; Rahman and Elder 2005). One of the acknowledged challenges of genetic studies in psoriatic arthritis is differentiating which factors predispose to arthritis versus psoriasis.

3.5.3 Non-genetic factors

Environmental factors implicated in the aetiology of, and susceptibility to, rheumatoid arthritis include i) non-genetic body factors, ii) infective agents and iii) non infective agents (Silman and Pearson 2002). Non genetic body (host) factors refer to hormonal and pregnancy influences. The decrease in joint symptoms reported by women during the post-ovulatory phase of the menstrual cycle and also during pregnancy is attributed to the elevated levels of oestradiol and progesterone (Ostensen *et al.* 1983). In contrast, the flare in symptoms of rheumatoid arthritis, frequently experienced post partum, is likely due to a drop in these hormonal levels (Costenbader and Manson 2008). Evidence suggests that the oral contraceptive pill delays the onset of the disease (Hannaford *et al.* 1990; Uhlig and Kvien 2005). However, these findings were not upheld in subsequent studies (Spector *et al.* 1991; Doran *et al.* 2004). There is also evidence that both nulliparity (Spector *et al.* 1990), and breastfeeding after first pregnancy contribute to a greater risk (Brennan and Silman 1994; Barrett *et al.* 2000). No association between post menopausal hormone therapy and incidence or severity has been conclusively demonstrated (Walitt *et al.* 2008). In summary, evidence in relation to the exogenous effects of oestrogen on the incidence and severity of rheumatoid arthritis remains conflicting (Costenbader and Manson 2008; Walitt *et al.* 2008). There is little conclusive evidence in relation to the role of infective agents in the cause of rheumatoid arthritis. It is suggested that the decrease in incidence and prevalence of rheumatoid arthritis in several populations over the years is indirect evidence of a causal

relationship between rheumatoid arthritis and an infective triggering agent (Jacobsson *et al.* 1994; Gabriel *et al.* 1999; Shichikawa *et al.* 1999). Direct evidence on the relationship between the onset of rheumatoid arthritis and infectious agents is inconclusive to date. The agents most usually implicated include the Epstein-Barr virus, parvovirus and bacterial agents such as Proteus, Mycoplasma and Yersinia (Silman and Pearson 2002).

Recent epidemiology studies have demonstrated a link between rheumatoid arthritis onset, its severity, and resistance to treatment, and the environmental risk factor, smoking (Hutchinson and Moots 2001; Kvien *et al.* 2006; Westhoff *et al.* 2008). Overall, there are surprisingly few studies on the role of diet. More recently, there is both interest and growing evidence on a potential protective role of omega-three fatty acids in rheumatoid arthritis, attributed to their beneficial role in inflammation (Volker *et al.* 2000).

The environmental triggers suggested to make a distinct contribution to the aetiology of psoriatic arthritis include infective agents and trauma (Bruce and Silman 2001). Scientific evidence that infective agents (bacterial or viral) may contribute to the development of psoriatic arthritis exists. This includes the identification of elevated levels of viral replication markers on serology, elevated level of hepatitis C antibodies when compared with controls, and the increased association between HIV and both psoriasis and psoriatic arthritis on case reports (Bruce and Silman 2001).

In psoriatic arthritis the evidence of the role of either a physical and psychological trauma as a precursor to the onset of inflammatory arthritis is stronger than for rheumatoid arthritis. The nature of the acute events implicated is as diverse as recent surgery, myocardial infarction, therapeutic abortion and poisoning. By definition all contribute both physical and psychological components of trauma (Bruce and Silman 2001). Psoriatic arthritis remains poorly understood with no distinct immunogenetic factors and some poorly understood environmental triggers. Exposures to a trauma and /or certain infective agents are the suggested and unverified most likely triggers of psoriatic arthritis (Pattison *et al.* 2008).

3.5.4 Summary of contributory factors

These inflammatory arthritides are regarded as multifactorial diseases with overlapping and distinct features resulting from the interaction of both genetic and environmental factors, which contribute to disease occurrence and expression. The main risk factors for the disease occurrence and severity include any combination of genetic susceptibility, gender, age, infectious triggers, smoking, and hormonal factors.

3.5.5 Clinical signs of rheumatoid arthritis

The key signs of early inflammatory joint disease in rheumatoid arthritis include swelling, tenderness, warmth, and painful movement (Gordon and Hastings 2004). Joint tenderness is the most sensitive physical sign of rheumatoid arthritis (Emery 1999). The joints most often involved early in the disease are the small joints of the hands and feet, commonly in symmetrical distribution, with gradual progression to the larger joints of the upper and lower limbs. Tendon sheath synovitis, predominately affecting the flexor tendon sheath of the hands, is another common finding (Bresnihan 2004). The degree of joint swelling evident may not correlate with the amount of active synovitis or pain expressed by the patient. Joint swelling may be peri-articular or intra-articular, the latter is associated with the presence of a joint effusion (Minnock 2002; Gordon and Hastings 2004).

3.5.6 Articular features of rheumatoid arthritis

The usual pattern of joint distribution or involvement includes the proximal interphalangeal joints (PIP), and the metacarpophalangeal joints (MCP) joints of the hands, wrists, elbows, shoulders, knees, ankles, subtalar, and metatarsophalangeal (MTP) joints of the feet. The cervical spine is the only characteristic axial location, with atlantoaxial subluxation a known complication (Eijk *et al.* 2006), and tempromandibular joints are frequently involved (Gordon and Hastings 2004). The radiographic hallmarks of chronic synovitis include periarticular osteoporosis, focal bone erosions at the joint margins and loss of joint space (Emery *et al.* 2008). Inadequately treated articular inflammation can lead to progressive weakening or destruction of collateral structures, including the associated joint

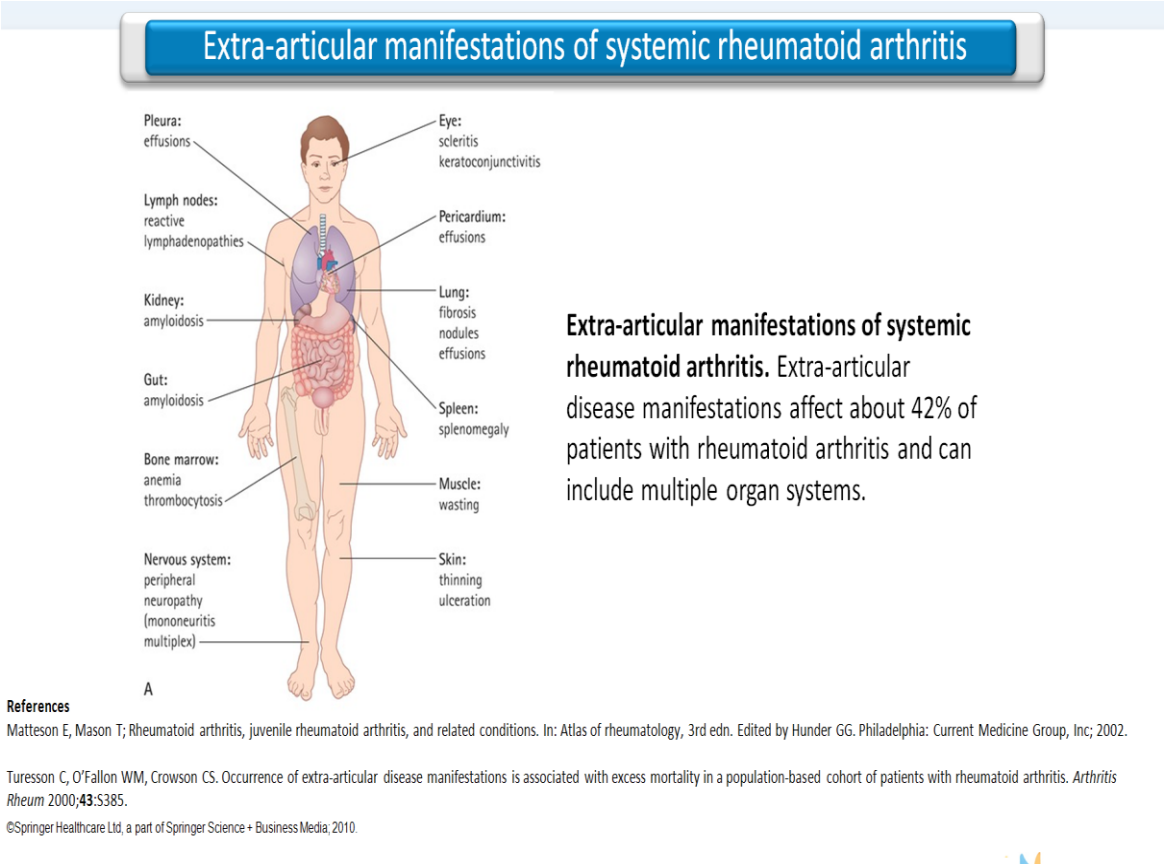
ligaments, tendons, cartilage, and bone. In addition, the pain associated with ongoing synovitis frequently leads to decreased range of movement at the affected joints. Initially, it is inflammation, and subsequently the progressive joint destruction, evident on x-ray, that drives disability in rheumatoid arthritis (Kirwan 2001). It is estimated that 90% of patients with rheumatoid arthritis become disabled within 20 years of disease onset (Emery *et al.* 2008).

While the recognised classic presentation of rheumatoid arthritis is a symmetric polyarthropathy of the small joint of the hands and feet it may also present with an extra-articular or non-articular presentation, such as a local bursitis, tenosynovitis, carpal tunnel syndrome, or a symmetric presentation with a diffuse polyarthralgia or polymyalgia (Gordon and Hastings 2004).

3.5.7 Extra-articular features of rheumatoid arthritis

Extra-articular features of rheumatoid arthritis affect over 40% of patients, and involve multiple organ systems (Figure 3-2). One of the most common extra-articular manifestations is the development of subcutaneous rheumatoid nodules. This feature, found in about 30% of patients with rheumatoid arthritis, is usually associated with the presence of a high titre rheumatoid factor antibody (Gordon and Hastings 2004). Rheumatoid nodules are regarded as a cardinal diagnostic feature, they have been shown to be a marker for more severe disease but often appear late in the disease. Studies show a two to fourfold increase in mortality in patients with extra-articular manifestations, such as rheumatoid nodules (Turesson *et al.* 2002; Gabriel *et al.* 2003). Early presence of rheumatoid nodules is regarded as a predictor of more severe extra-articular manifestations. The many and varied extra-articular manifestations occur in a small but important subset of patients with rheumatoid arthritis (Gabriel *et al.* 2003) (Figure 3-2).

Figure 3-2: Extra-articular manifestations of systemic rheumatoid arthritis



Reproduced by kind permission of Springer Science and Business Media (Matteson *et al.* 1997; Turesson *et al.* 2002) (Appendix 2).

3.5.8 Systemic extra-articular features of rheumatoid arthritis

Systemic features of rheumatoid arthritis also referred to as constitutional or extra-articular manifestations, such as fatigue, fever, anorexia and weight loss, may occur early in the course of the disease. In some cases these features persist, and can predominate the articular symptoms. Elderly patients in particular may present with polymyalgias, polyarthralgias and profound fatigue (Gordon and Hastings 2004). Laboratory indicators of systemic involvement in rheumatoid arthritis include elevated acute-phase reactants; erythrocyte sedimentation count (ESR); C-reactive protein (CRP); anaemia; thrombocytopenia; elevation of certain liver function tests (Matteson *et al.* 2003). The multi-system features found in a small but important subset of patients (Gabriel *et al.* 2003), are presented in

Figure 3-2 and summarised in Table 3-2. When present these can confound the correct diagnosis of this disease that has no single diagnostic pathognomonic feature.

Table 3-2: Possible extra-articular and systemic manifestations of rheumatoid arthritis

General Fever Lymphadenopathy Anorexia /Weight loss Fatigue (Crosby 1991; Belza *et al.* 1993; Belza 1995; Wolfe *et al.* 1996; Barry 2003; Matteson *et al.* 2003).	**Cardiac** Pericarditis Myocarditis Nodules on valves Ischaemic heart disease (Harris 2001; Bacon *et al.* 2002; Goodson 2002; Kaplan 2006; Solomon *et al.* 2006; Naranjo *et al.* 2008).
Dermatological Palmar erythema Subcutaneous nodules Vasculitis (leukocytoclastic) (nailfold infracts) Digital ulceration Leg ulceration Raynaud's phenomenon (Firestein 2001; Turesson *et al.* 2002; Gabriel *et al.* 2003; Matteson *et al.* 2003; Gordon and Hastings 2004; Calguneri *et al.* 2006; Highton *et al.* 2007)	**Neuromuscular** Entrapment neuropathy Peripheral neuropathy Mononeuritis multiplex Cervical myopathy Steroid mypopathy (Neva *et al.* 2000; Matteson *et al.* 2003; Emery *et al.* 2008).
Ocular Episcleritis Scleritis Choroid and retinal nodules Sjogrens syndrome (keratoconjunctivitis sicca) (10-35%) Steroid related cataracts Drug induced retinopathies (Drosos *et al.* 1988; Gordon and Hastings 2004).	**Hematological/Biochemistry** Normocytic hypochromic anemia Thrombocytosis Felty's syndrome Lymphomas Serology : Positive for rheumatoid factor and anti-CCP antibodies (30%) (Sibley *et al.* 1991; Turesson *et al.* 2002; Turesson *et al.* 2007; Kaiser 2008; Smitten *et al.* 2008; Brown and Boers 2010; Swales *et al.* 2010)
Pulmonary Pleuritis Pulmonary nodules Interstitial lung disease Bronchiolitis obliterans (Drosos *et al.* 1988; Gordon and Hastings 2004; Nannini *et al.* 2008)	**Renal** Drug induced renal toxicity Renal vasculitis Glomerulonephritis Amyloidosis (Harris 2001)
Hepatic Elevated liver enzymes Drug induced hepatotoxicity(Matteson *et al.* 1997; Matteson *et al.* 2003; Chakravarty *et al.* 2008).	**Others** Hodgkin disease Non-Hodgkin lymphoma and Squamous cell skin cancer Osteoporosis (Hemminki *et al.* 2008; Smitten *et al.* 2008)

3.5.9 Clinical signs of psoriatic arthritis

Clinical signs of psoriatic arthritis are similar to those of rheumatoid arthritis. These key signs of an early inflammatory joint disease include swelling, tenderness, warmth, and painful movement. It is recognised that the associated joint tenderness found in psoriatic arthritis is less than that found with rheumatoid arthritis (Gladman 1998). Clinical signs peculiar to psoriatic arthritis include psoriasis, nail changes such as nail pitting -small indentations in the nail, and onycholysis (separation of the nail from the nail bed), tendonitis and dactylitis. The range of signs and symptoms can vary from patient to patient dependant on both the variety and severity of presentation.

3.5.10 Articular features of psoriatic arthritis

Psoriatic arthritis is a heterogeneous condition; patients may present with any combination of diverse features at different stages of their disease. Five classic presentations of joint involvement are described (Moll and Wright 1973b) (Table 3-3).

Table 3-3: Five classic presentations of joint involvement in psoriatic arthritis

1	Inflammatory distal interphalangeal (DIP) joint involvement
2	Peripheral polyarthritis: often symmetrical as seen in rheumatoid arthritis
3	Spondyloarthropathy: spondylitis & sacro-ilitis (spinal & sacro-iliac joint inflammation)
4	Asymmetrical, oligoarthritis (involvement of four joints or less)
5	Arthritis mutilans: characterised by destruction and “telescoping” of the fingers

3.5.11 Extra-articular features of psoriatic arthritis

Any of these aforementioned presentations may be accompanied by the most frequently described extra-articular manifestations of psoriatic arthritis listed in (Table 3-4) (Gladman *et al.* 2005a). Unlike rheumatoid arthritis, psoriatic arthritis is not a multisystem disorder, the predominant extra-articular manifestations include, psoriasis, dactylitis, enthesitis and nail lesions (Helliwell and Wright 1997; Gladman *et al.* 2005a).

Table 3-4: Extra articular and systemic features of psoriatic arthritis

1	Any form of psoriasis (or a personal or family history of psoriasis)
2	Dactylitis- sausage shaped digits
3	Enthesitis: (inflammation of the entheses, the sites where tendons or ligaments insert into bone)
4	Tenosynovitis (tendon sheath inflammation)
5	Features common to the spondyloarthropathies: mucous membrane lesions, ocular lesions (conjunctivitis, iritis, uveitis), urethritis, colitis, aortic root dilatation, HLA-B27 association

It is noteworthy that fatigue is seldom listed as either an extra articular or systemic feature of psoriatic arthritis. More commonly it is referred to as a symptom or a comorbidity (Mease 2007) of this disease entity. Its recognition as an important feature of psoriatic arthritis is recent (Chandran *et al.* 2007; Gladman *et al.* 2007b). It is acknowledged that fatigue is often underrated by treating physicians (Kavanaugh and McHugh 2007).

3.5.12 Diagnoses of rheumatoid arthritis and psoriatic arthritis

Distinguishing a chronic illness such as rheumatoid arthritis from other self-limiting conditions can be difficult. There are no early onset disease specific features; the characteristic hallmarks of the disease develop over time. A salient characteristic of rheumatoid arthritis is its chronic and enduring nature; therefore it is not unusual that the diagnosis of rheumatoid arthritis is delayed for months or even years. With the lack of a disease-specific feature or test the diagnosis of rheumatoid arthritis remains a composite of clinical and investigational features (Quinn *et al.* 2004).

The study of psoriatic arthritis has lagged behind other inflammatory arthropathies; it still lacks universal agreement on diagnostic criteria and therefore can pose a diagnostic challenge for physicians (Bruce 2004; Helliwell and Taylor 2005). Recognised experts in the field have been known to disagree when a diagnosis involves cases lacking characteristic clinical features (Symmons *et al.* 2006). A typical challenging diagnostic case might be a patient with a seronegative symmetrical polyarthritis and psoriasis. Similar to rheumatoid arthritis there is no clinical, radiological, or immunological feature that is pathognomonic of psoriatic arthritis.

3.5.13 Laboratory investigations: markers of inflammation

Laboratory measures or markers of a biological activity within the body such as inflammation, that indirectly measure a disease state, are known as surrogate measures. Inflammation is a biological activity; in rheumatoid arthritis and psoriatic arthritis this is prolonged, and disproportional (Emery *et al.* 2008). Therefore, measures of inflammation, called acute-phase reactants, are used as surrogate markers of this inflammatory process. The most widely used biological markers to establish the presence of inflammation and disease activity are laboratory blood measurement of the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Elevated liver enzymes, specifically serum aspartate aminotransferase (AST) and alkaline phosphatase, and a fall in serum albumin level frequently parallel the elevated erythrocyte sedimentation rate, and C-reactive protein (Emery *et al.* 2008).

There are no diagnostic laboratory tests for psoriatic arthritis. During disease flares, acute-phase reactants or markers which reflect the inflammatory process include, elevated erythrocyte sedimentation rate; C-reactive protein and fibrinogen; anaemia of chronic disease, and hypoalbuminaemia. The majority of cases will be rheumatoid factor negative on serology (90-95%) (Troughton and Morgan 1994; Bruce 2004).

3.5.14 Clinical diagnosis

There is no one clinical, radiological, or immunological features that is pathognomonic of rheumatoid arthritis, therefore, the diagnosis is largely clinical, made by recognising the pattern of signs and symptoms. Diagnosis of early rheumatoid arthritis is dependent on good history taking skills and physical examination rather than on any special investigations (Emery *et al.* 2002; Barry 2003; Gordon and Hastings 2004). The standard procedure for diagnosis includes documentation of history and pattern of joint swelling and pain, physical examination, laboratory tests for measures of inflammation such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP); evidence of specific auto antibodies, such as rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) antibodies (Combe *et al.* 2007; Brown and Boers 2010); radiographic imaging of affected

joints, and presence of extra-articular disease and co-morbid conditions (Emery 1999; Barry 2003).

Table 3-5: Clinical and investigational diagnostic features of rheumatoid arthritis (Emery 1999)

Standard Procedures for Diagnosis	**Presenting Symptoms**
History of swelling /pain	Joint pain
Physical examination	Joint swelling: Small joints, symmetrical
Laboratory tests: Elevated ESR, CRP	Joint stiffness
Laboratory evidence of specific auto-antibodies (rheumatoid factor and anti-CCP) (Swales *et al.* 2010)	Difficulty making a fist, especially on waking
Imaging evidence of damage/inflammation (radiography, MRI, ultrasonography)	Fatigue
Extra-articular disease and co-morbid conditions	Good response to anti-inflammatory drugs
Physical Signs	**Clinical Features**
Evidence of synovitis	Evidence of synovitis
Joint tenderness (positive squeeze test)	Inflammation (ESR/CRP)
Joint swelling/effusions/warmth	Serological abnormalities
Symmetrical involvement	Rheumatoid factor, anti CCP auto antibodies
Nodules (occasionally)	X-ray evidence (joint space increased due to effusion, soft tissue swelling, periarticular osteoporosis, characteristic erosions)
	MRI / Ultrasound abnormalities
	Systemic features: Fatigue, Fever, Weight Loss

The composite clinical and investigational features of rheumatoid arthritis summarised in Table 3-5, provide a framework for diagnosis, and for monitoring and management of the course of this chronic rheumatic autoimmune disease.

A history indicative of rheumatoid arthritis includes prolonged early morning stiffness that improves with activity, polyarthritis, polyarthralgia (pain in many joints), and fatigue. Examination findings consistent with a diagnosis of rheumatoid arthritis include symmetric polyarthritis and rheumatoid nodules. Radiographic changes include periarticular osteopenia, joint space loss, and erosions. Although most serology studies are neither

sensitive nor specific for rheumatoid arthritis they help exclude mimics of rheumatoid arthritis and confirm the presence of inflammation (Emery 1999)

The original and most frequently used diagnostic criteria for psoriatic arthritis are those presented in Table 3-6, as described by Moll and Wright, (1973b).

Table 3-6: Original diagnostic criteria for psoriatic arthritis

1	An inflammatory arthritis; peripheral arthritis and / or sacroilitis or spondylitis
2	The presence of psoriasis
3	The (usual) absence of serological tests for rheumatoid factor

The composite clinical and investigational features of psoriatic arthritis are summarised in Table 3-7. These provide a framework for diagnosis and for monitoring and management of the course of this distinct disease entity. Patients with psoriatic arthritis usually present with the typical hallmarks of an inflammatory arthritis; joint pain, swelling, erythema and varying degrees of joint stiffness, fatigue, impaired function, other defining features of this disease entity including enthesitis, dactylitis, psoriasis, nail changes, distal interphalangeal involvement, and iritis (Moll and Wright 1973b; Gladman 1998; Gladman *et al.* 2005a; Helliwell and Taylor 2005).

The standard procedure for diagnosing includes documentation of history and pattern of articular and extra-articular features, physical examination, and laboratory testing to establish serological status of rheumatoid factor and markers of inflammation (Bruce 2004). Despite many other diagnostic and classification criteria having been proposed over the years for psoriatic arthritis there is a lack of validation criteria, such as those developed for use in rheumatoid arthritis. It is anticipated that the relatively new ClASsification of Psoriatic Arthritis (CASPAR) criteria (Appendix 3) will become the standard for all future clinical studies (Taylor 2007).

Table 3-7: Clinical and investigational diagnostic features of psoriatic arthritis

Standard Procedures for Diagnosis	**Presenting Symptoms**
History of pain/swelling, psoriasis Physical examination Laboratory tests/ evidence: Elevated ESR, CRP (Gladman *et al.* 1998), Rheumatoid factor negative, HLA-B27 association, Hyperuricaemia Hypercholesterolemia (Bruce 2004) Imaging evidence of damage/inflammation (radiography, MRI, ultrasonography) Extra-articular disease and co-morbid conditions	Asymmetrical joint pain, swelling, stiffness Variable clinical distribution- distal interphalyngeal (DIP), spinal, sacroiliac joints, asymmetrical oligoarthritis, symmetrical polyarthritis (Gladman *et al.* 2004). Fatigue (Gladman *et al.* 2007a; Husted *et al.* 2009) Established psoriasis (75%) Good response to anti-inflammatory drugs
Physical Signs	**Clinical Features**
Evidence of synovitis-joint tenderness (positive squeeze test), joint swelling/effusions/warmth Asymmetrical joint involvement DIP joint involvement (40%) (Gunal *et al.* 2009) Dactylitis (16-48%) (Rothschild *et al.* 1998) Enthesitis and Tenosynovitis Psoriasis (Gunal *et al.* 2009) Nail changes (98%) Spondyloarthritis (>50%) Features common to the spondyloarthropathies: mucous membrane lesions, ocular lesions (conjunctivitis, iritis, uveitis), uretritis, colitis, aortic root dilatation (Bruce 2004; Gladmann 2005)	Evidence of synovitis and psoriasis Inflammation (ESR/CRP) Rheumatoid factor negative HLA B27 positivity +/- X-ray evidence: including DIP joint involvement +/- erosive changes, asymmetric distribution, involvement of entheseal sites with proliferative new bone formation e.g plantar fascia, tendo-Achilles insertion, osteolysis of phalanx, periostitis of metacarpals and metatarsals MRI / Ultrasound abnormalities Systemic features: fatigue, fever, weight loss.

3.5.15 Management of inflammatory arthritis

For the purpose of a rational yet comprehensive overview of the area of modern pharmacological approaches to treatment, and of the aim of modern therapies, the focus will be confined to early inflammatory arthritis. For convenience rheumatoid arthritis was taken as the index condition for inflammatory arthritis. The rationale for this being that despite discrete differences in pathogenesis, the drug therapies used to treat rheumatoid arthritis and psoriatic arthritis are the same (Helliwell and Taylor 2008). The overarching goal in the management of both disease entities is reversal of the pathogenic process; this is the basis of modern therapeutic biologic therapies (Mease *et al.* 2005c).

In clinical practice early inflammatory arthritis is often undifferentiated. Early arthritis may develop into established rheumatoid arthritis or into another distinct arthropathy, such as psoriatic arthritis. It may resolve spontaneously, or the diagnosis may remain unclear. A three step process is recommended in order to improve the diagnosis and outcome in arthritis. The first step is the identification of the presence of inflammatory arthritis, the next is distinguishing between definite diagnoses of arthritis (for example, rheumatoid arthritis, psoriatic arthritis), and the third step is estimation of the risk of developing persistent or erosive irreversible arthritis and to propose an optimal treatment strategy (Combe *et al.* 2007).

3.5.16 Therapeutic goals

Management of rheumatoid arthritis is defined as all organisational, diagnostic, medical and educational procedures related to patients seeking help for arthritis of a peripheral joint (Combe 2007). The ultimate therapeutic goal in the treatment of rheumatoid arthritis is to induce complete remission, unfortunately this rarely occurs (Emery 1999). Therefore, the goals of management of rheumatoid arthritis include the suppression of the signs and symptoms of synovitis, the prevention of structural damage, maintenance of function and a reduction in mortality. Twelve key recommendations for the management of early arthritis and early rheumatoid arthritis were developed by The European League against Rheumatism (EULAR) based on evidence in the literature and expert consensus (Combe *et*

al. 2007) (Table 3-8). These provide a comprehensive summary of evidence based management including all steps in the process from early referral, diagnosis, prognosis and treatment, and are presented, as published.

3.6 Modern Pharmacological Approaches to Treatment

Three major types of drug therapy are used in the treatment of inflammatory arthritis: non steroidal anti-inflammatory drugs, disease modifying anti-rheumatic drugs, and glucocorticoids. Non-steroidal anti-inflammatory drugs provide symptomatic relief of pain, stiffness and inflammation without influencing the causes of inflammation. Disease modifying anti-rheumatic drugs act by a variety of pathways with the common mechanism of inhibiting the main pro-inflammatory cytokines (Emery 1999). Inhibition of pro-inflammatory cytokines, mediators of inflammation, results in a decrease of disease activity, reduction in joint damage, preservation of function and improvement in systemic symptoms. Glucocorticoids have actions similar to both non-steroidal anti-inflammatory drugs and disease modifying anti-rheumatic drugs; use in clinical practice is largely confined to short term for symptomatic relief. On account of their potential side effect profile, their long term use as disease modifying drugs is no longer recommended, therefore, they have been largely superseded by modern biologic disease modifying therapies (Hoes *et al.* 2009; van der Goes *et al.* 2010). Evidence based treatment guidelines (Table 3-9 and Figure 3-3) have been formulated and published by experts in both disease entities (Kavanaugh and Ritchlin 2006; Combe *et al.* 2007).

Table 3-8: Final set of recommendations on the management of early arthritis based on both evidence and expert opinion

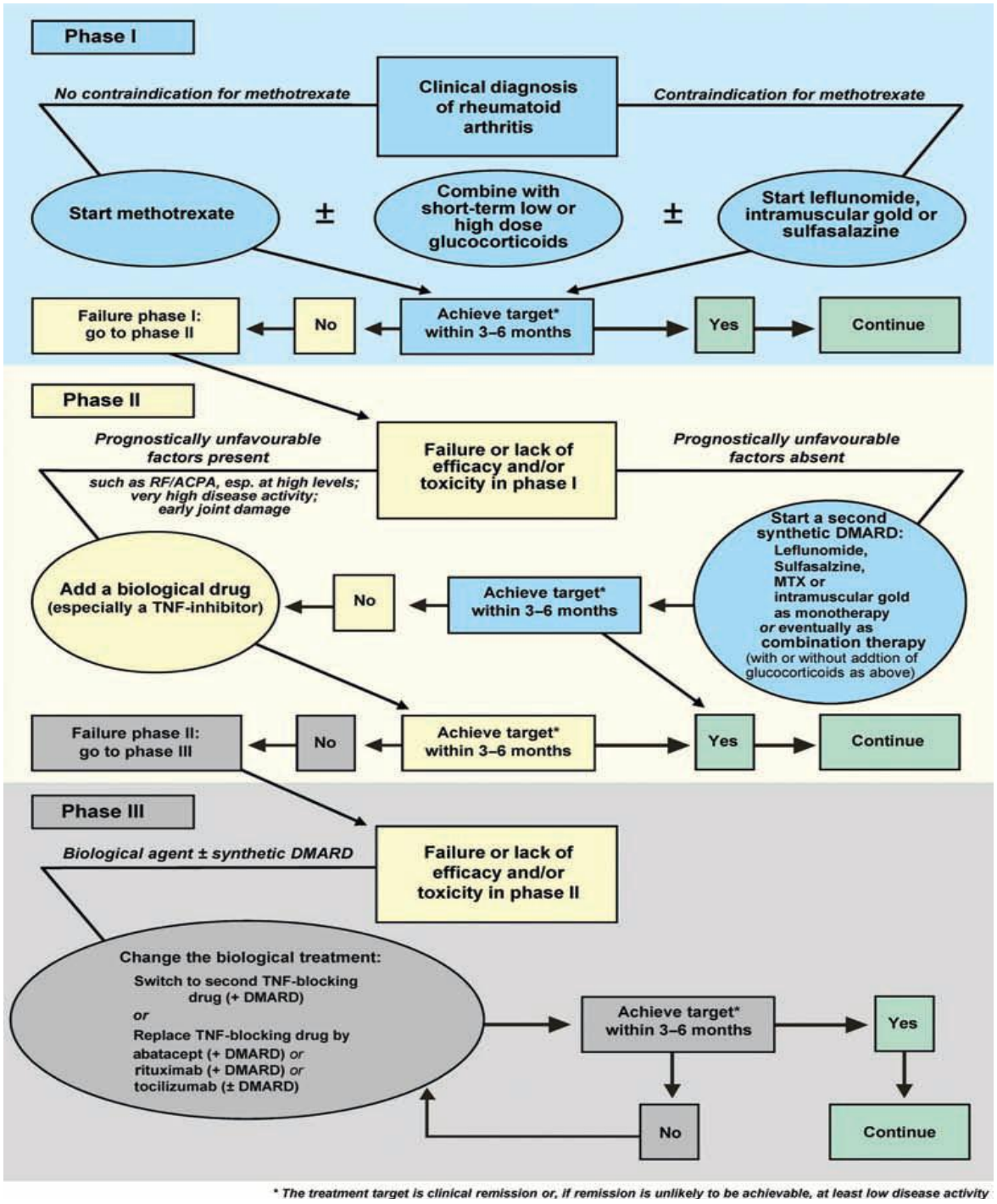
1	Arthritis is characterised by the presence of joint swelling, associated with pain or stiffness. Patients presenting with arthritis of more than one joint should be referred to, and seen by, a rheumatologist, ideally within six weeks after the onset of symptoms
2	Clinical examination is the method of choice for detecting synovitis. In doubtful cases, ultrasound, power Doppler, and MRI might be helpful to detect synovitis.
3	Exclusion of diseases other than rheumatoid arthritis requires careful history taking and clinical examination, and ought to include at least the following laboratory tests: complete blood cell count, urinary analysis, transaminases, anti-nuclear antibodies.
4	In every patient presenting with early arthritis to the rheumatologist, the following factors predicting persistent and erosive disease should be measured: number of swollen and tender joints, ESR or CRP, levels of rheumatoid factor and anti-CCP antibodies, and radiographic erosions.
5	Patients at risk of developing persistent or erosive arthritis should be started with DMARDs as early as possible, even if they do not yet fulfill established classification criteria for inflammatory rheumatological diseases.
6	Patient information concerning the disease and its treatment and outcome is important. Education programmes aimed at coping with pain, disability, and maintenance of work ability may be employed as adjunct interventions.
7	NSAIDs have to be considered in symptomatic patients after evaluation of gastrointestinal, renal, and cardiovascular status.
8	Systemic glucocorticoids reduce pain and swelling and should be considered as adjunctive treatment (mainly temporary), as part of the DMARD strategy. Intra-articular glucocorticoid injections should be considered for the relief of local symptoms of inflammation.
9	Among the DMARDS, methotrexate is considered to be the anchor drug, and should be used first in patients at risk of developing persistent disease.
10	The main goal of DMARD treatment is to achieve remission. Regular monitoring of disease activity and adverse events should guide decisions on choice and changes in treatment strategies (DMARDs including biological agents).
11	Non-pharmaceutical interventions such as dynamic exercises, occupational therapy, and hydrotherapy can be applied as adjuncts to pharmaceutical interventions in patients with early arthritis.
12	Monitoring of disease activity should include tender and swollen joint count, patients' and physician's global assessments, ESR, and CRP. Arthritis activity should be assessed at one to three month intervals, for as long as remission is not achieved. Structural damage should be assessed by radiographs of hands and feet every 6 to 12 months during the first few years. Functional assessment (for example, HAQ) can be used to complement the disease activity and structural damage monitoring.

CRP, C reactive protein. anti-CCP anti-cyclic citrullinated peptide. DMARD, disease modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; MRI, magnetic resonance imaging. (Combe *et al.* 2007)

3.6.1 Disease modifying anti-rheumatic therapies: non-biologic and biologic agents

Disease modifying anti-rheumatic drugs fall into two separate groups: the traditional non-biological drugs or synthetic agents, and the modern biologic disease modifying drugs (Saag *et al.* 2008). The most commonly used non-biological drugs include methotrexate (the main anchor drug) (Chakravarty *et al.* 2008), hydxochloroquin, sulfasalazine and luflonomide, alone or in various combinations (Grigor *et al.* 2004). The principle biologic disease modifying therapies include; infliximab, etanercept, adalimumab, abatacept and rituximab (Saag *et al.* 2008). Early intervention with non biologic disease modifying anti-inflammatory drugs is the cornerstone of treatment and in the early stages may halt the progressive synovitis, associated joint destruction and progressive disability. However, only a minority of patients achieve a good response on non-biologic therapies alone (Grigor *et al.* 2004). Evidence based treatment guidelines were recently formulated and published by EULAR (Table 3-9) with respect to rheumatoid arthritis (Smolen *et al.* 2010b).

Table 3-9: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying anti-rheumatic drugs
(Smolen *et al.* 2010b).



Algorithm based on the European League Against Rheumatism recommendations on rheumatoid arthritis management. DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; RF/ACPA, rheumatoid factor/anti-citrullinated peptide antibodies; TNF, tumour necrosis factor. *The treatment target is clinical remission or, if remission is unlikely to be achievable, at least low disease activity.

These comprehensive recommendations provide a framework for standardising care for patients with rheumatoid arthritis. Overarching principles state that patients with rheumatoid arthritis need to be treated by a rheumatologist and that treatment should aim at best care, based on a collaborative decision between patients and rheumatologist (Gibofsky and Yazici 2010). Remission or at least a low disease activity is the recommended treatment goal summarised in a three phase approach: phase I comprises the initiation of disease modifying treatment on diagnosis; phase II address patients who fail to achieve the treatment target with these steps. This second phase stratifies patients according to poor prognostic factors indicating the need to use combination non–biologic agents and or biologic agents; phase III relates to patients for whom the first biologic therapy fails. Moreover, this three phase process emphasise the importance of close monitoring of patients using composite disease activity measures and the adaptation of treatment strategies within preferably 3-months, at most 6-months, to ensure treatment aim of complete remission or a low disease activity state, is reached (Kavanaugh and Fransen 2006; Ritchlin 2007; Smolen *et al.* 2010b).

In relation to psoriatic arthritis treatment guidelines are those of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), presented in (Figure 3-3), (Mease *et al.* 2005a; Ritchlin *et al.* 2008). Both sets of guidelines represent the collaborative workings of rheumatologists, and dermatologists in conjunction with patients. The stated aim is to provide best care and outcome for patients with inflammatory arthritis regardless of economic or political considerations (Ritchlin *et al.* 2008; Smolen *et al.* 2010b).

Figure 3-3: Evidenced based treatment guidelines for the management of psoriatic arthritis in clinical practice.

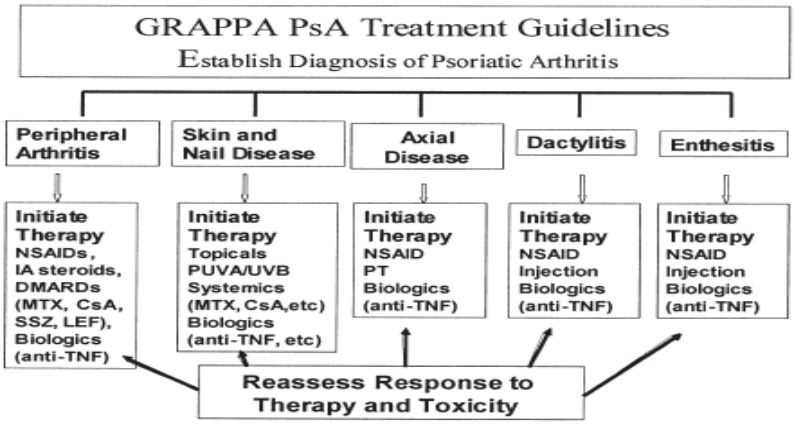


Fig. 1. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) treatment guidelines.
(From Kavanaugh *et al.*: GRAPPA Guidelines for the treatment of psoriatic arthritis. *J Rheumatol* 2006; 33: 1417-21).

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3.6.2 Summary of therapeutic management

The treatment of patients with inflammatory arthritis is better now than in previous decades on account of the more widespread early and intensive treatment approach, the extensive use of the disease modifying anti-rheumatic drug, methotrexate, the availability of novel therapeutic biologic therapies, the availability of evidence based treatment guidelines and recognition that regular monitoring of patients with quantitative measures improves disease outcome (Gibofsky and Yazici 2010). Rheumatoid arthritis and psoriatic arthritis are chronic diseases characterised not only by biomedical signs but also by an array of patient reported symptoms. For this reason it is recommended that regular patient monitoring should also include patient reported outcome measures as part of a strategy for achieving optimal outcome and best care (Pincus *et al.* 2006; Gibofsky and Yazici 2010). Monitoring disease course and effectiveness of treatment, of the respective conditions of rheumatoid arthritis and psoriatic arthritis, in order to optimise patient outcome, is next presented.

3.7 Measuring Disease Outcome in Inflammatory Arthritis

3.7.1 How to monitor disease course

Measures which monitor the course of disease were originally classified into Process (swollen joints, tender joints, pain, patient global assessment, CRP) and Outcome (health assessment questionnaire, radiographic scores) variables. Process variables measure disease activity in the here and now, while outcome variables measure the impact of the disease activity over a period of time (Fries *et al.* 1980; Kirwan 1992). Some variables measure a mixture of both; functional capacity for example is influenced by current disease activity as well as irreversible joint damage from past disease activity, while acute-phase reactants (laboratory biochemical measures of inflammation) are pure process outcomes, and radiographic damage scores are solely outcome measurements (van Riel 1992). An alternate classification was subsequently proposed because the original terms of reference were used by many different authors in a variety of ways. This divides variables into 3 major groups: i) measures of disease activity ii) measures of tissue damage and iii) measures of health status. The first two groups refer to the disease pathology and the third group refers to the impact of the disease on the patient. The outcome of treatment interventions in the short term is best measured by disease activity and long term outcome is more usually evaluated by measures of tissue damage or patients health status. Disease activity in inflammatory arthritis is generally represented by a set of variables or outcome measures which can be reported individually or as part of an index of disease activity (van Gestel and Stucki 1999). Although originally developed for use in clinical trial situations these measures are currently in widespread use in both clinical trials and in clinical practice for the purpose of monitoring disease outcome.

3.7.2 Why assess and monitor disease outcome

The purpose of assessing and monitoring disease status in rheumatoid arthritis and psoriatic arthritis is twofold, firstly, to evaluate, and secondly, to manipulate the disease process (van der Heijde *et al.* 1990) in order to improve patient outcome. Timely diagnosis and timely

institution of therapy has a significant impact on the preservation of joint structure and function, and has implications for the long-term overall health and functional status of the patient. If control of disease is achieved within the first several months the rate of radiographic progression and joint destruction is minimised (Bresnihan 2004; Emery *et al.* 2008). Although the best outcomes in rheumatoid arthritis are obtained with early aggressive disease control, it is never too late to intervene if ongoing inflammation is present. This emphasises the need for continuous assessment of disease activity and response to treatment in longitudinal clinical observational studies (Emery *et al.* 2008). Furthermore, advances over the last decade, in novel and expensive biologic therapy treatments for inflammatory arthritis, has highlighted the need for a consensus on assessment tools and outcome measures for these autoimmune diseases (Gladman 2005). The key functions of outcome measurements are threefold: 1) to compare results from different drug trials, 2) to evaluate disease activity and, 3) to quantify improvement or response to therapeutic intervention for the purpose of achieving the overarching goal of disease remission or at least a state of minimal disease activity in real life situations (Combe *et al.* 2007; Smolen *et al.* 2010b).

3.7.3 Assessment of disease activity and defining improvement in rheumatoid arthritis and psoriatic arthritis in clinical practice

The clinical characteristics of disease activity in rheumatoid arthritis were traditionally measured by an array of different variables covering aspects of the disease process and outcome in order to evaluate therapeutic interventions (van Riel 1992). To improve the comparability of study results international consensus was reached on a core set of outcome measures: The American College of Rheumatology (ACR) core set of disease activity measures (Felson *et al.* 1993) (Table 3-10).

Table 3-10: American College of Rheumatology disease activity measures for rheumatoid arthritis trials: core set outcome measures

	Disease Activity Measures
1.	Tender joint count
2.	Swollen joint count
3.	Patient's assessment of pain
4.	Patient's global assessment of disease activity
5.	Physician's global assessment of disease activity
6.	Patient's assessment of physical function
7.	Acute-phase reactant value (biochemical measure of inflammation; CRP, ESR)[#]
8.	For trial duration ≥ 1 year and agent being tested as a disease modifying anti-rheumatic drug (DMARD) also perform: Radiographic or imaging technique (measure of tissue damage)

*See Appendix 6 for recommended assessment techniques, [#] C-reactive protein, ESR erythrocyte sedimentation rate

The three ways by which these outcome measures can be reported: - i) individually, ii) as part of an index of disease activity, and iii) as part of an index of improvement (EULAR and ACR20), listed in

Table 3-11, will be described.

Table 3-11: Measures of outcome and improvement criteria

	Outcome Measures	**Methods of Reporting**
1	The ACR core set outcome measures-	8-individually reported variables
2	The disease activity score (DAS)-	Composite score of 3 or 4 core set variables
3	The EULAR response criteria-	Response index based on changes in DAS
4	ACR20 criteria for improvement-	Response index (%) in 5 core set variables

3.7.4 The American College of Rheumatology core set of outcome measures

The American College of Rheumatology preliminary core set outcome measures for rheumatoid arthritis were agreed as the minimum number of endpoints which should be used in all clinical trials (Tugwell *et al.* 1994). This core set of outcomes includes the first 7 disease status measures listed in Table 3-10. Together, these variables measure a broad range of clinical disease characteristics in rheumatoid arthritis, from both the perspective of the patient and the physician. In so doing, the core set of outcome measures demonstrate content validity. The individual measures demonstrate discriminant validity and are moderately sensitive to change (Felson *et al.* 1993). The core set outcomes contain measures of symptoms which have the potential to reflect the biology of the disease (swollen and tender joints counts). Many also predict important long-term outcomes in rheumatoid arthritis, including physical disability, radiographic damage and premature death (Felson *et al.* 1993). These core set measures are independent variables which have been shown to exert a causal influence on other symptoms such as the patient reported outcome, fatigue (Minnock and Bresnihan 2008). To promote uniformity of assessment and so enhance validity, recommendations about what instruments to use for each outcome measure were made by EULAR (Scott *et al.* 1993), and by the ACR (Felson *et al.* 1995b) (Appendix 6).

A consensus on core domains for psoriatic arthritis that should be included in randomised clinical trials and clinical observational studies on patient cohorts was reached at OMERACT in 2007. The six core domains agreed include: peripheral joint activity count, skin activity, pain, patient global assessment, physical function, and health related quality of life. Other domains were agreed as important but not mandatory for inclusion in all clinical trials or observational studies. These include: spinal disease, dactylitis, enthesitis, fatigue, nail disease, radiography, physician global assessment, and acute phase reactants (Gladman *et al.* 2007b).

Variable numbers of joint counts are included in various systems from a comprehensive 28 swollen and tender joint count to a more extensive 68 and 66 in the assessment of rheumatoid arthritis, or 78 and 76 swollen and tender joint count respectively, in the

assessment of psoriatic arthritis (Felson *et al.* 1995a; van Riel and Scott 2004; Mease *et al.* 2005a; Mease *et al.* 2005b). These joint counts are then combined with the other traditional core set outcome measures of disease activity (Felson *et al.* 1993; Mease *et al.* 2005a).

These core outcome measures can be reported individually; they are also reported as part of an index of disease activity called the disease activity score in both disease entities.

3.7.5 Disease Activity Score

The disease activity score is a composite score derived from the core set outcome measures. The need for a single gold standard score for measuring disease activity led to the development of the composite scores, the Disease Activity Score (DAS) and the modified Disease Activity Score 28 (DAS28) (van Riel 1992; Prevoo *et al.* 1995; van Gestel and Stucki 1999). The Disease Activity Score (DAS) was developed in Nijmegen in the 1980's to measure disease activity in patients with rheumatoid arthritis (http://www.das-score.nl). The original DAS is a standardised, composite outcome measure of disease activity derived from combining four of the core set of outcome measures, i) swollen joint count, ii) tender joint count, iii) acute-phase reactants (CRP/ESR), and iv) general health assessment on a visual analogue scale. The original DAS equation incorporates a 44 joint count that grades the tenderness of each joint on a scale of 0-3 (van der Heijde *et al.* 1992; van Riel 2001). Disease activity is represented as a continuous score giving a single value of disease activity between 0 and 10. The advised time to completion is 5-8 minutes (Fransen *et al.* 2003). While it is extensively validated for use in clinical trials its easy use also makes it a valuable tool for assessment of disease activity in daily clinical practice.

However, for feasibility and ease of use in clinical practice, additional equations have been developed. The DAS28 is analogous to the DAS, but has a reduced joint count of 28. This more user friendly scale incorporates a swollen and tender joint count based on a 28 joint count, instead of the original 44 joints. The total DAS28 scale has 4 items (DAS28 4 variable ESR or CRP), or three if the general health assessment is omitted (DAS28 3 variable ESR or CRP), it can also be calculated using CRP instead of ESR (van Riel). This modified DAS, the DAS28, has been shown to be as valid as disease activity scores that use

more comprehensive and extensive joint scores (Prevoo *et al.* 1995). The advised time to completion is 3-5 minutes which favours its use in clinical practice (Fransen *et al.* 2003).

Although the original DAS was developed in a cohort of patients with early rheumatoid arthritis both the DAS and the DAS28 have subsequently been found to be equally applicable to patients with longer standing disease. It had also been shown to perform comparably to the adult ACR improvement criteria in clinical trials (Prevoo *et al.* 1996). Serial measurements of the DAS and DAS28 are strong predictors of physical disability and radiological progression (van der Heijde *et al.* 1992). Both DAS and DAS28 discriminate between patients with high and low disease activity and between patients on active and placebo treatment arms in clinical trials (Wijnands *et al.* 1992).

The DAS28 scale is summarised in Table 3-12. Scores range between 0 and 10, indicating how active the rheumatoid arthritis is at that time point. A DAS28 above 5.1 means high disease activity whereas a DAS28 below 3.2 indicates low disease activity. Remission is achieved by a DAS28 lower than 2.6 (http://www.das-score.nl), (comparable to the original American Rheumatology Association (ARA) remission criteria) (Fransen *et al.* 2004).

Table 3-12: Disease Activity Score 28

		Thresholds of Disease Activity			
DAS28	**Score Range**	**Remission**	**Low**	**Moderate**	**High**
	0-10	**< 2.6**	**≤ 3.2**	**>3.2 and ≤ 5.1**	**> 5.1**

Advantages of the DAS or DAS28 for use in clinical practice relate to the fact that both are i) a continuous measure of disease activity that can be used over time and ii) an absolute measure of disease state at one point in time. The DAS28 is used extensively to measure patients' response to treatment particularly with the advent of new and expensive biologic therapies (Ledingham *et al.* 2005). For this purpose alone it facilitates the communication of the disease status of an individual patient between providers, as well as providing a quality measure of treatment. It is the DAS which is the most useful single gold standard measure for assessment of disease activity in daily clinical practice (van Riel 2001). The ready availability of DAS pocket calculators ensures its feasibility of use. A response index, known as the EULAR Response Criteria, based on the DAS was also developed,

derived from information on initial, current, and change over time in disease activity scores (van Gestel *et al.* 1996).

3.7.6 EULAR response criteria

The EULAR response criteria, developed from the DAS, (van Gestel *et al.* 1996; van Gestel and Stucki 1997), are the most extensively used in the evaluation of improvement in patients with either rheumatoid arthritis or psoriatic arthritis both in clinical practice and clinical trials.

These DAS-based European (EULAR) response criteria were developed in order to measure individual response/improvement in clinical trials (Table 3-13) (van Gestel *et al.* 1996). The EULAR response criteria include not only change in disease activity but also current disease activity. The criteria classify individual patients into three categories of responders: good, moderate, and non-responders. To be classified as responders, patients must demonstrate a significant reduction in DAS as well as a low current disease activity (Fransen and van Riel 2005). All three response criteria were developed using DAS28 (van der Heijde *et al.* 1992), and validated against the EULAR criteria using the original DAS and, using the comprehensive (44 joints) as well as the 28 joint counts (Wijnands *et al.* 1992; Davidson *et al.* 2003). The validity of the response/improvement criteria using the 28 joint count versus the criteria using the more comprehensive joint count has been demonstrated. Furthermore, any discrepancy in responder status was less than 5%. Comparing the DAS28 from one patient on two different time points, it is possible to define improvement or response as shown in Table 3-13.

Table 3-13: EULAR Response Criteria

DAS28 Improvement	***> 1.2***	***> 0.6 - ≤ 1.2***	***≤ 0.6***
Present DAS28			
< 3.2	Good Response	Moderate Response	No Response
3.2 - 5.1	Moderate Response	Moderate Response	No Response
>5.1	Moderate Response	No Response	No Response

In patients with psoriatic arthritis the discriminant properties of these DAS-based response criteria, which were developed for use in rheumatoid arthritis (van Gestel *et al.* 1996), have been reported from studies of two different TNFi therapies (Antoni *et al.* 2005a; Kavanaugh and Fransen 2006; Coates *et al.* 2008).

3.7.7 American College of Rheumatology definition of improvement–ACR20

The core set outcome measures was further utilised to develop a single index of improvement: - the American College of Rheumatology Improvement Criteria in rheumatoid arthritis (ACR20) (Felson *et al.* 1995b). An ACR20 is defined as at least 20% improvement in both the tender joint count and swollen joint count and at least 20% improvement in 3 of the 5 other core set outcome measures. The ACR20 focused on improvement in individual patients rather than mean improvements in groups of treated patients. This means that critical analysis of why response to treatment by individual patients differs is possible (Anderson *et al.* 2000). As improvement options evolved, clinical trials have raised the thresholds for improvement to ACR50 and ACR70 (Felson 2007). However, the original ACR 20% threshold for improvement in a variety of core set measures has superior discriminant validity than the higher thresholds of ACR 50% or 70% improvement (Felson *et al.* 1998). The ACR20, ACR50, ACR70 percent are regarded as dichotomous (response yes or no) of the individual response, which means they capture either the presence of, or the absence of, the response in percentage terms. It is argued that the dichotomous nature of these criteria is less sensitive to overall changes in disease states than are continuous measures such as the Disease Activity Score (DAS) (van Gestel *et al.* 1996). Use in a clinical practice setting is advised against, other validated measures such as the EULAR response criteria are recommended above the ACR response criteria (Furst *et al.* 2008).

A psoriatic arthritis specific response index has been developed, the psoriatic arthritis response criteria (PsARC) (Clegg *et al.* 1996), and its discriminant properties between placebo and treatment groups is demonstrated (Mease *et al.* 2005a). However, the ACR20 response criteria have been shown to be a more stringent outcome measure in this group of patients. The discriminant properties of both the ACR50 and ACR70 are also

demonstrated in all of the trials with anti-tumour necrosis factor (TNFi) agents. More recently, the validity of the DAS28 for use in patients with psoriatic arthritis prescribed TNFi therapy has been demonstrated (Vander Cruyssen *et al.* 2007; Saber *et al.* 2010), and the EULAR criteria have shown more discriminate properties than the ACR20, which in turn performed better than the PsARC (Fransen *et al.* 2006).

3.7.8 Clinical remission in inflammatory arthritis

While the goal of treatment in rheumatoid arthritis is remission there is no consensus on a definition of remission (Pinals *et al.* 1982; Makinen *et al.* 2006). Definitions of clinical remission have evolved with the advances in modern pharmacological therapies. The earliest definition included six clinical criteria (Table 3-14), agreed by experts to yield optimal discrimination. These preliminary criteria require that 5 out of these 6 criteria be fulfilled (Makinen *et al.* 2005). Comparative studies have shown that a cut-off level of the DAS of 1.6 (Prevoo *et al.* 1996) or a DAS28 of 2.6 (Fransen *et al.* 2004) corresponded with being in remission following these criteria. However, in both of these comparative studies a 'modified' set of preliminary criteria for clinical remission was used as the clinical variable fatigue was not measured (Prevoo *et al.* 1996; Repping-Wuts *et al.* 2007). Reasons why fatigue was lost form this original core set of measures over time could be attributed to lack of clarity around its prevalence in patients versus health subjects, lack of consensus on definitions and measurement tools, and non-recognition of the value of patients reported outcomes in health care.

Table 3-14: Preliminary criteria for clinical remission in rheumatoid arthritis
(Pinals *et al.* 1982)

1.	Morning stiffness duration ≤ 15 minutes
2.	No fatigue
3.	No joint pain
4.	No joint tenderness or pain on motion
5.	No soft tissue swelling in joints or tendon sheaths
6.	ESR ≤ 30mm/hour for a female /20mm/hour for a male.

The lack of a good definition of remission in rheumatoid arthritis for daily clinical need, as well as for use in clinical trials, is a recognised challenge for outcome measurement (Makinen *et al.* 2005). Moreover, of interest is that this early criteria compiled by medical consensus identified the absence of fatigue as a necessary criteria for clinical remission. Yet almost three decades later the debate continues as to whether fatigue, a patient reported outcome, should be regarded as an inflammatory variable and included as a core outcome measure in all clinical trials (Pollard *et al.* 2005; Dayer and Choy 2010). This also highlighted the need for an agreement on validated assessment instruments for fatigue outcome in both rheumatoid arthritis and psoriatic arthritis to permit comparative analysis across studies.

Recently, an ACR and EULAR collaboration on defining remission in rheumatoid arthritis proposed one of two provisional definitions, based on the core set outcome measures, for use in clinical trials. These are either a compilation of four core outcome measures when scores on: (i) a tender joint count, swollen joint count, C-reactive protein (in mg/dl), and patient global health (0-10 scale) are all ≤ 1; or (ii) an index based measure when the score on the Simplified Disease Activity Index, [SDAI= sum of 28 tender joint count, 28 swollen joint count, patient global assessment (0-10 scale), physician global assessment (0-10) scale, and CRP level (mg/dl)], is ≤ 3.3 (Aletaha and Smolen 2005). It is recommended that both be uniformly applied and widely used in rheumatoid arthritis clinical trials (Felson *et al.* 2011a; Felson *et al.* 2011b) for comparative purposes.

As with rheumatoid arthritis, there is much discussion around the definition of remission in psoriatic arthritis (Kavanaugh and Fransen 2006), spurred on by the treatment advances over the last decade (Ritchlin 2007). For psoriatic arthritis patients it is stated that a stage of no symptoms and no impact on function can be considered to be disease remission (Kavanaugh and Fransen 2006). Difficulty in reaching a consensus is attributed to the heterogeneity of clinical subsets and disease manifestations as well as the identified need for consensus and validation of outcome measures (de Vlam and Lories 2008). The efficacy of modern therapies, particularly TNFi therapies, has raised the likelihood of clinical remission and even cure for patients with psoriatic arthritis (Antoni *et al.* 2005b; Wong and Lebwohl 2005; Kavanaugh *et al.* 2007). Meanwhile, in the absence of criteria for defining remission patients are still assessed in clinical practice using the disease

activity and improvement criteria originally designed for use in rheumatoid arthritis (de Vlam and Lories 2008), the EULAR response criteria (Kavanaugh and Fransen 2006; Leeb *et al.* 2007). However, studies have validated their use in this diagnostic group of patients (Vander Cruyssen *et al.* 2007; Coates *et al.* 2008; Saber *et al.* 2010).

3.7.9 Patient reported outcomes

During the recent process of development of a definition of remission in rheumatoid arthritis for application in clinical trials, patient reported outcomes were reviewed (Felson *et al.* 2011a; Felson *et al.* 2011b). The working group comprised expert members of ACR, EULAR, and OMERACT, and included expert patients from the OMERACT group. The process involved analysis of the core outcomes from clinical trial data to select a definition of remission while examining the added contribution of patient-reported outcomes and the ability of candidate measures to predict later good radiographic and functional outcomes. The analysis concluded that patient-reported outcomes, namely, patient global health assessment and patient-reported pain, were statistically significant predictors capable of discriminating between treatments, after controlling for physician-reported measures such as swollen and tender joint counts. However, this process revealed that fatigue, a patient reported outcome, was not evaluated in most clinical trials published over the last decade, including those used in the development of the remission definition. The group anticipated that over the course of several years these data related to fatigue will become available and meanwhile advocated qualitative and quantitative work on the concept of patient assessed 'absence of disease'. This concept could be compared with the newly proposed definition of remission in due course (Felson *et al.* 2011a; Felson *et al.* 2011b). This comprehensive review of trial data provided robust evidence of the importance of patient-reported measures in the assessment of disease outcome.

3.7.10 Summary of Outcome Measurement

Ongoing assessment and monitoring of disease status in inflammatory arthritis is necessary to positively influence these chronic diseases and their implications for the long-term overall health and functional status of patients. Both early and sustained management is

advocated which emphasises the need for continuous assessment of outcome. In turn this highlights the need for a consensus on appropriate assessment tools and outcome measures for these autoimmune diseases. Such a consensus has been reached as is evidenced by the core set outcomes and the associated derived measures of disease activity, response criteria, and more recently a definition of remission. Traditional outcome measurements focused on the clinician's assessment of the patient, and on expert agreement on what outcome should be measured without direct inclusion of patients in this process of consensus and decision making. However, over the last decade it has been acknowledged that patients and physicians can hold different perspectives and attempts are being made to incorporate outcomes important to patients for frequent measurement in clinical trials or clinical practice. Therefore, the next section of this review focused on the patient perspective on outcome in rheumatoid arthritis and psoriatic arthritis in order to frame the problem under study. This was done by integrating the literature on both biomedical mechanism and patients' experiences of fatigue in these respective disease entities.

3.8 Patients' Perspectives: Symptoms of Rheumatoid Arthritis and Psoriatic Arthritis

A comprehensive literature search was undertaken to identify publications related to patients' perspectives, outcome measurement, and fatigue in both rheumatoid arthritis and psoriatic arthritis. The databases used were Medline (Medicine, Dentistry, and Nursing) from 1980; CINHAL (Cumulative Index to Nursing and Allied Health) from 1982, and PsycINFO (Psychology) from 1980; the final search date was April 2nd 2011.

The most prominent symptoms reported by patients with rheumatoid arthritis include pain and swelling, usually affecting several joints simultaneously, difficulty in making a fist, and difficulty in walking, particularly early morning on first waking or after periods of immobility (Bresnihan 2004; Gordon and Hastings 2004). Pain is accepted as the most dominant symptom of rheumatoid arthritis (Kazis *et al.* 1983; Emery 1999; Heiberg and Kvien 2002; Minnock *et al.* 2003b). Patients frequently complain of morning stiffness, of variable duration, or after brief periods of inactivity. This phenomenon is a characteristic feature of inflammatory joint disease or synovitis (Liang and Sturrock 1997). In clinical practice symptoms are usually interpreted in terms of patients' functional ability to perform self-care and other daily home, work and recreational activities. It is the patient's functional status which provides the best clinical sign of both current and future well being (Wolfe 2000; Geuskens *et al.* 2007; Shanahan *et al.* 2008; Zirkzee *et al.* 2008).

Fatigue is the other major constitutional symptom of rheumatoid arthritis frequently reported by patients. It has been reported as the most disturbing component of the disease (Crosby 1991; Belza *et al.* 1993; Belza 1995; Wolfe *et al.* 1996; Emery 1999; Hewlett *et al.* 2005b; Mancuso *et al.* 2006). It is the one symptom experienced almost universally and as frequently as daily by patients with rheumatoid arthritis (Hewlett *et al.* 2005b; Repping-Wuts *et al.* 2008a). Patients frequently rate the impact and importance of fatigue as similar to that of the most recognised dominant symptom of pain (Minnock and Bresnihan 2004; Hewlett *et al.* 2005b; Kirwan *et al.* 2008).

The course of psoriatic arthritis is usually characterised by flares and remissions. Like rheumatoid arthritis the common symptoms include: pain aggravated by movement, swelling and tenderness of the joints and surrounding soft tissue, reduced range of movement, morning stiffness and fatigue (Helliwell and Wright 1997). Early morning symptoms of stiffness and pain predominate and usually subside during the day. Fatigue is a common symptom of psoriatic arthritis (Schentag *et al.* 2000; Chandran *et al.* 2007; Husted *et al.* 2009); in one study patients reported less vitality than those with rheumatoid arthritis (Husted *et al.* 1998) although results in this regard lack consistency (Helliwell and Ruderman 2007).

3.8.1 Fatigue in inflammatory arthritis: a patient reported outcome

Rheumatoid arthritis is generally regarded as the index disease of the inflammatory arthropathies (Fransen and van Riel 2009); psoriatic arthritis was seen as an atypical variant of rheumatoid arthritis before gaining it own unique identity, within the last fifty years (Gladman *et al.* 2005a). Traditionally, the most common and frequently studied symptom of these collective arthropathies was the symptom of pain. The earliest studies on fatigue in rheumatoid arthritis were published twenty odd years ago (Tack 1990a, 1990b; Crosby 1991; Belza *et al.* 1993; Belza 1995). However, it is only within the last decade that fatigue secured itself as a variable of interest among rheumatology researchers and clinicians in rheumatoid arthritis and psoriatic arthritis (Kirwan *et al.* 2003; Gladman *et al.* 2005b). This development occurred when the established international consensus conference on outcome measures in rheumatology (OMERACT) invited patients, those with the disease, to become research partners (Carr *et al.* 2003; Kirwan *et al.* 2003; Hewlett *et al.* 2005a; Kirwan *et al.* 2005b; Kirwan *et al.* 2007). A specially convened Patient Perspective Workshop at OMERACT involved a series of formal and informal work group meetings of patients, clinician and researchers. These focused on identifying, and agreeing on, outcomes of interventions in rheumatoid arthritis from the perspective of patients (Kirwan *et al.* 2003). Following this OMERACT initiative fatigue secured its place internationally on the rheumatology research agenda on patients' perspectives on symptom priorities for research (Kirwan *et al.* 2003; Kirwan *et al.* 2005b). Thus the concept of adopting the patients' perspective in identifying novel outcomes and measurement instruments of relevance

originated and has since become inculcated into research and clinical practice within rheumatology (Kirwan *et al.* 2003; Kirwan *et al.* 2005a; Kirwan *et al.* 2005b). Initial focus was on the experience of fatigue in those with rheumatoid arthritis only, more recently, fatigue as a patient reported outcome measure is being evaluated in other rheumatology disease entities such as in psoriatic arthritis (Gladman *et al.* 2007b).

3.8.2 Prevalence of fatigue

Precise data on the prevalence of fatigue in both rheumatoid arthritis and psoriatic arthritis is scant. Most papers relevant to the topic begin by acknowledging how common the symptom is based more on clinical and anecdotal evidence than on formal robust epidemiological studies (Rupp *et al.* 2004). The general consensus is that this symptom is a universal experience among patients with inflammatory arthritis. It is suggested that approximately 90% of patients with rheumatoid arthritis experience fatigue as often as daily (Pinals *et al.* 1982; Crosby 1991; Belza *et al.* 1993; Belza 1995; Katz 1998; Neville *et al.* 1999; Carr *et al.* 2003); studies have shown that this fatigue is clinically relevant for 40-80% of patients with rheumatoid arthritis attending specialists services (Wolfe *et al.* 1996; Pollard *et al.* 2006).

Studies in psoriatic arthritis on the prevalence of fatigue are even sparser, the limited literature suggests that a quarter of patients experience severe or overwhelming fatigue and that as many as 57% report at least moderate fatigue (Schentag *et al.* 2000; Chandran *et al.* 2007).

3.8.3 Characteristics of the symptom of fatigue in inflammatory arthritis

The term ‘symptom’ is widely used when referring to the concept of fatigue so for this reason to begin with a definition of this term is appropriate. A symptom is defined as a subjective experience reflecting changes in biopsychosocial functioning, sensations or cognition of the individual, while in contrast, a sign is defined as any abnormality indicative of disease and detectable by the individual or by others (Harver and Mahler 1990). Fatigue is a recognised symptom of inflammatory arthritis, namely rheumatoid

arthritis and psoriatic arthritis, frequently attributed to the systemic nature of these auto-immune driven conditions (Tack 1990a; Alarcon 1995; Wolfe *et al.* 1996; Matteson *et al.* 2003; Pollard *et al.* 2006; Husted *et al.* 2009). Quantitative and qualitative studies show that fatigue is a symptom of great importance to patients with inflammatory arthritis (Katz 1998; Minnock and Bresnihan 2004; Hewlett *et al.* 2005a; Hewlett *et al.* 2005b; Repping-Wuts *et al.* 2008a).

3.8.4 Clinicians' perspectives

The earliest definitions of fatigue largely represent the clinicians' perspectives. One such definitions of this phenomenon in rheumatoid arthritis proposed fatigue 'as the subjective sensation of generalised tiredness or exhaustion' (Tack 1990b). This definition was applied in an American (US) pilot study which examined the symptom of fatigue by triangulating findings from three separate sources: from a mood questionnaire, specifically developed visual analogues scales for pain and fatigue, and from qualitative interviews on fatigue. The author explained the concept of subjectivity as a self recognised phenomenon embedded in the individual's own evaluation of their current state, and cited the Shaw et al., 1962, physiological explanation for the term 'generalised' as a 'sensation that encompasses the person as a whole…not restricted to specific anatomical structures, regions or functions' (Tack 1990b).

More recent definitions of fatigue, such as that proposed by The Patient-Reported Outcomes Measurement Information System (PROMIS) initiative: Dynamic Tools to Measure Health Outcomes from the Patients Perspective, are derived from combined nursing, cancer, and outcome measurement literature (Stewart *et al.* 1992; North American Nursing Diagnosis Association 1996; Glaus 1998). The goal of this North American PROMIS network, a National Institutes for Health initiative, is to build and validate common, accessible item banks to measure key symptoms and health concepts applicable to a range of chronic conditions. The purpose of this initiative is to enable efficient and interpretable clinical trial research and clinical practice application of patient-reported outcome (PROMIS 2010). From within this context of outcome measurement the more contemporary definition is: -

> ‘fatigue at its highest level is defined as an overwhelming, debilitating, and sustained sense of exhaustion that decreases one's ability to carry out daily activities, including the ability to work effectively and to function at one's usual level in family or social roles. Similar subjective feelings, yet fewer behavioural impacts, are associated with lower levels of fatigue. Fatigue is divided conceptually into the experience of fatigue (such as its intensity, frequency and duration), and the impact of fatigue upon physical, mental and social activities’ (PROMIS 2010).

Discussion around fatigue in psoriatic arthritis draws largely from the primary research in rheumatoid arthritis and utilises the definition from nursing diagnoses (Chandran *et al.* 2007). The latter define fatigue as an overwhelming, sustained sense of exhaustion and decreased capacity for physical and mental work (North American Nursing Diagnosis Association 1996). Modern definitions of fatigue recognise its subjective nature and encompass both defining attributes along with the outcome of the experience of this symptom in patients with inflammatory arthritis. Increasingly, patients’ perspectives are being incorporated in order to reach consensus on definitions and moreover on meaning of symptoms, in health care outcome research.

3.8.5 Patients perspective

With the advent of the patient perspective initiative within the rheumatology research community, the focus has been more on understanding the meaning of fatigue and the fatigue experience, than agreeing on a precise definition (Kirwan *et al.* 2005b). Appropriately, qualitative research has been undertaken de novo (Hewlett *et al.* 2005b; Repping-Wuts *et al.* 2007; Nikolaus *et al.* 2010a). Prior to this only one qualitative study was published; this seminal work by Tack in the US explored fatigue in patients with rheumatoid arthritis (Tack 1990a). Together these four qualitative studies provide insight into the fatigue experience such as the subjective meaning of fatigue and its perceived causes, the broad consequences, and management approaches, as reported by patients.

In these studies the terms most commonly used by patients to convey the meaning of fatigue are reported; fatigue is described as a tiredness in the original US study (n=12), and as a sense of tiredness and heaviness in the more recent UK study (n=15) (Tack 1990a; Hewlett *et al.* 2005b). In common, all four studies highlight the variability in the nature of fatigue in terms of its onset, unpredictability, duration and severity, and moreover, how difficult it is to describe this symptom. Patients experienced fatigue as frustrating and overwhelming, different from normal tiredness. This can lead to the phenomenon of 'wipe out' when the patient has to stop all activity (Hewlett *et al.* 2005b). Moreover, fatigue was described as an unearned, unpredictable and overwhelming symptom (Hewlett *et al.* 2005b; Repping-Wuts *et al.* 2008a). The perceived causes of fatigue reported were pain, functional challenges and restrictions, and disturbed sleep; the main conditions under which patients experienced fatigue were states of disease activity, and stress. Across all studies, participants drew a distinction between fatigue related to, and fatigue experienced prior to developing, rheumatoid arthritis; on balance, the cause of fatigue was attributed to rheumatoid arthritis (Tack 1990a; Hewlett *et al.* 2005b; Repping-Wuts *et al.* 2008a). These findings were from samples of patients where neither their state of disease activity nor treatment regimen was predetermined, therefore, they did not address the interrelationship between fatigue and disease activity. Hence, exploration of the fatigue experience in patients with low disease activity, following a specific treatment regimen, will provide further insight into the meaning of fatigue, from a more homogeneous group.

The meaning of fatigue was better represented in all studies through descriptions of its broad ranging consequence. The consequences of fatigue exerted a multidimensional impact including feelings of frustration, helplessness and hopelessness (emotional), (Tack 1990a), strained relationships (social), cognitive impairment, and physical interference with participation in life (Hewlett *et al.* 2005b; Repping-Wuts *et al.* 2007). One Dutch study (n=31) was also unique in highlighting some positive outcomes reported such as learning to adjust personal goals and life expectations, and being able to sleep easier (Nikolaus *et al.* 2010b). Fatigue was reported as frequent, extreme and multidimensional; consequently, it pervaded all aspects of life resulting in disruption and distress (Hewlett *et al.* 2005b; Repping-Wuts *et al.* 2008a). While the emotional consequences were in accord across the four studies, of interest, was the unique finding that negative daily emotions as a consequence of fatigue were more frequently experienced by females with multiple daily

work roles (Nikolaus *et al.* 2010b). Mobility and function were impeded for males and females alike (Hewlett *et al.* 2005b). Gender and age related difference were reported in only one study where on account of fatigue females had more negative experiences in terms of stress, maintaining social contacts, work performance and employment (Nikolaus *et al.* 2010b). In this same study only a few older patients reported no fatigue related consequences; only women reported variable ability in successfully coping with fatigue (Nikolaus *et al.* 2010b). In order to minimise the broad reaching consequences of fatigue further information on contributory factors is required. It is appropriate to further explore factors which influence fatigue outcome in the context of both the formal recognition of fatigue as an important patient reported outcome, and the availability of improved pharmacological therapies for the treatment of rheumatoid arthritis.

Management strategies, reported in three studies, were found to be multidimensional in nature, had variable success in relation to outcome, and were largely self-initiated (Tack 1990a; Hewlett *et al.* 2005b; Repping-Wuts *et al.* 2007). Patients used a combination of physical, mental and social activities to manage their fatigue; they availed of rest and pacing, distraction and downward comparison, emotional and social support, as ways of dealing with their fatigue. The major contradistinction between USA (Tack 1990a), and UK participants (Hewlett *et al.* 2005b), was that UK patients employed neither social nor emotional support. This expressed negative attitude in relation to fatigue among the UK population is akin to the sense of hopelessness and helplessness which was an outcome of fatigue among the USA participants (Tack 1990a). Whether this sense of hopelessness and helplessness is a consequences or driver of this chronic symptom merits evaluation. Moreover, because of the multidimensional nature and consequences of fatigue, self-management capability and needs, and related outcome warrant further exploration.

Like clinicians, patients seldom acknowledged their fatigue as a symptom, believing it cannot be treated; those patients who did felt it was dismissed by their clinician (Hewlett *et al.* 2005b; Repping-Wuts *et al.* 2008a); patients perceiving fatigue to be part of the disease for which nothing could be done (Repping-Wuts *et al.* 2008a). Only one of these studies looked at bottlenecks in professional care and management of fatigue (Repping-Wuts *et al.* 2008a). The few participants who had received professional advice found its generic nature to be impractical (Repping-Wuts *et al.* 2008a). Therefore, it would be interesting to re-

evaluate whether such practices and behaviours by patients and clinicians alike have changed for the better since fatigue assessment has been formally recommended (Kirwan *et al.* 2007).

In summary, similar descriptors, and experiences related to consequences, and management of fatigue emerged from all four qualitative studies. Patients experienced fatigue as frustrating and overwhelming, different from normal tiredness, unearned and unpredictable (Hewlett *et al.* 2005b; Repping-Wuts *et al.* 2008a). All studies found the consequences of fatigue to include physical, emotional, and cognitive components that permeated every sphere of life including roles and relationships, mood, mobility and activities (Tack 1990a; Hewlett *et al.* 2005b; Repping-Wuts *et al.* 2008a; Nikolaus *et al.* 2010b). Enquiry into management strategies identified limited self-management capability and, moreover, minimal professional interest and support in management of this symptom (Hewlett *et al.* 2005b; Repping-Wuts *et al.* 2007). Inter and intra-individual difference, in both experience and impact of fatigue, and some positive consequences were also identified (Nikolaus *et al.* 2010b).

While patient characteristics in relation to age, gender and disease duration were comparable across all studies, nonetheless, transference of findings is restricted due the diversity in methodological techniques, and design limitations, within the respective studies. Only the UK study had experiencing fatigue as an inclusion criterion, and provided information on participants current fatigue levels (Hewlett *et al.* 2005b), therefore, the nature of participant current fatigue levels was largely unknown. Involvement of patients as research partners in the study design, analysis and interpretation of the results, contributes to study findings (US Department of Food and Human Services 2009; Nicklin *et al.* 2010b), and so transferability of qualitative research (Polit and Beck 2010b); this methodological approach was adopted in only one of these studies (Hewlett *et al.* 2005b). The broad rheumatology community derives its insight into the lived experience of fatigue from these four qualitative studies from diverse populations and cultures. All four studies used different data analysis techniques including descriptive content analysis using a coding framework (Tack 1990a), grounded theory techniques (Hewlett *et al.* 2005b), and a combination of qualitative and quantitative description (Repping-Wuts *et al.* 2007; Nikolaus *et al.* 2010a). Insight into and understanding of fatigue will grow further with

verification of findings in different contexts, varied times, and within different people through study replication (Polit and Beck 2010b). Exploration of fatigue among patients with documented high levels of persistent fatigue despite a good disease response to modern TNFi therapies will provide an additional perspective, study replication in this new population will explore the relevance and importance of themes previously highlighted. This will serve to enhance generalisation / transference of findings, and the existing evidence base for current clinical practice (Polit and Beck 2010b). Findings will therefore be more relevant to the modern era of biologic therapies so further enriching the existing knowledge base.

3.8.6 Contributory factors to fatigue in inflammatory arthritis

The date the elucidation of contributory factors to fatigue in inflammatory arthritis has been the subject of limited primary research studies on fatigue. Those conducted have focused mainly on patients with rheumatoid arthritis (Tack 1990b; Crosby 1991; Belza *et al.* 1993; Wolfe *et al.* 1996). Studies on fatigue in patients with psoriatic arthritis are fewer and more recent (Chandran *et al.* 2007; Husted *et al.* 2009; Husted *et al.* 2010). The crux of most debates on predictors and correlates of fatigue centres on whether fatigue is solely attributable to disease activity (Crosby 1991), represented by clinician-reported inflammatory variables such as swollen and tender joint counts, and acute-phase reactants (CRP); the alternate predictors and contributing factors proposed include patient-reported disease related factors such as pain, functional status, and more generic, non-disease specific, factors like psychological, and social issues, mood, sleep, and socio-demographics, (Tack 1990b, 1990a; Crosby 1991; Belza *et al.* 1993; Stone *et al.* 1997; Huyser *et al.* 1998). These clinician–reported and patient–reported factors will be reviewed in turn.

3.8.7 Clinician-reported biological mechanisms as the causal pathway to fatigue

The earliest expert agreed criteria for clinical remission in rheumatoid arthritis listed the absence of fatigue as a criterion capable of discriminating between patients in remission and an active disease state (Pinals *et al.* 1982). Nonetheless, it is also contended that ‘it is

almost a tenet of faith that fatigue is associated with disease activity' (Wolfe *et al.* 1996). This later conclusion was drawn mainly from cross sectional studies (Crosby 1991; Belza *et al.* 1993; Wolfe *et al.* 1996), these measured fatigue at one single point therefore cause and effect cannot be determined. Comparison between these studies is also restricted as different fatigue measurements were used. With the advent of biologic drug therapies, over the last decade, this debate has intensified. Unsolicited reports from patients of profound improvement in fatigue levels following treatment with TNFi agents brought the symptom of fatigue to the fore clinically (Wolfe and Michaud 2004). As a consequence, measures of fatigue were formally included in subsequent clinical trials on patients with rheumatoid arthritis (Weinblatt *et al.* 2003; Wells *et al.* 2007, 2008; Strand *et al.* 2009). This debate in support of fatigue as an inflammatory variable contends that fatigue in inflammatory arthritis is a consequence of the auto-immune inflammatory response.

The acute phase inflammatory response in both rheumatoid arthritis and psoriatic arthritis is coordinated through the release of the pro-inflammatory cytokines (interleukin (IL)-1, IL-6, IL-15, IL18 and TNFα), resulting in prolonged, disproportional inflammation (Emery *et al.* 2008). IL-6 is known to negatively influence fatigue, sleep, and concentration in healthy volunteers. Recent studies have demonstrated a correlation between IL-6 production and reports of fatigue in patients with rheumatoid arthritis (Dayer and Choy 2010). Targeted biologic therapies against IL-6 in active rheumatoid arthritis have demonstrated a clinically relevant improvement in fatigue levels (Genovese *et al.* 2008). Similarly, significant improvement in fatigue levels following TNFi therapy has been demonstrated in randomised controlled trials in rheumatoid arthritis (Strand *et al.* 2009), and in longitudinal study of separate cohorts of patients with rheumatoid arthritis and psoriatic arthritis (Pollard *et al.* 2006; Minnock *et al.* 2009; Minnock *et al.* 2010).

The correlation between laboratory markers of inflammation (acute-phase reactants ESR and CRP) and fatigue levels is inconsistent (Wolfe *et al.* 1996; Huyser *et al.* 1998; Pollard *et al.* 2006; Bergman *et al.* 2009), however. One study examined correlates of fatigue with the inflammatory marker ESR in patients with rheumatoid arthritis, and also in patients with two non-inflammatory rheumatic conditions (osteoarthritis and fibromyalgia). The 3 patient groups had similar R^2 and predictors for fatigue, namely pain, sleep disturbance and low mood, accounting for 90% variance in fatigue (Wolfe *et al.* 1996), concluding that

fatigue was not related to inflammation. Another study showed weak/fair correlations between fatigue and ESR (r = 0.071), swollen joint count (r = 0.112), tender joint count (r = 0.294), physician global assessment of disease activity (r = 0.384), and DAS28 (r = 0.399), but strong correlations with patients global assessment of disease activity (r = 0.567), again concluding that inflammatory components contribute minimally to fatigue in rheumatoid arthritis (Bergman *et al.* 2009). Moreover, the one longitudinal study which found improvements in fatigue levels reported by patients, following 3-months of either synthetic or biologic disease modifying agents, showed this largely correlated with improvements in pain (r = 0.63, $p < 0.001$; r = 0.65, $p < 0.0010$), and in DAS28 scores (r = 0.69, $p < 0.001$; r = 0.43, $p < 0.019$), respectively (Pollard *et al.* 2006). While it is suggested that the change in fatigue scores observed in clinical trials of biologic agents are more likely to reflect improvement in other disease related factors such as pain, function and psychological status, rather than any direct effect on cytokine activity (Wolfe and Michaud 2004; Pollard *et al.* 2006), further evidence is required. Most studies to date which examined this causal relationship were cross sectional in nature; results from the one longitudinal exception should be interpreted with caution on account of the small sample size (n=30), and limited follow-up of only two timepoints 3-months apart (Pollard *et al.* 2006).

In the case of patients with psoriatic arthritis an 8-year longitudinal study (n=390), which collected fatigue data on at least two occasions, showed higher ESR to be significantly associated with higher fatigue levels (t= 5.671; $p < 0.0001$), number of active joints (t= 9.478; $p < 0.0001$), and number of swollen joints (t= 6.930; $p < 0.0001$), while ever use of biologic agents was associated with lower levels of fatigue (t= -3.401; $p < 0.001$), over time. Although these clinical measures of disease activity were shown to be related to fatigue over time, this relationship disappeared in the context of disability and pain. However, this conclusion is drawn from a limited evidence base; experts in the area of psoriatic arthritis have called for longitudinal studies to further discern the relationship between fatigue and demographics, health status, and disease related factors (Husted *et al.* 2009).

The methodological quality of existing studies where fatigue was included as an outcome varies in design, duration, and use of measurement instruments. Therefore, findings lend themselves more to discussion rather than to synthesis of results. Further

robust longitudinal studies in patients with inflammatory arthritis are required, particularly in the context of modern efficacious biologic disease modifying therapies (Michaud *et al.* 2007), in order to further clarify the relationship between fatigue and the conventional measures of disease activity and outcome. Moreover, all future studies of fatigue experience in inflammatory arthritis should follow a standardised approach to measurement to enhance consistency of findings, and study comparison.

3.9 Patient-reported disease related factors as the causal pathway to fatigue

Other variables are implicated in the causal pathway of fatigue in inflammatory arthritis. These include the patient-reported disease related factors; pain, functional ability, and disturbed sleep.

Pain is the most dominant symptom of inflammatory arthritis and frequently implicated in the causal fatigue pathway. One of the first formal reports of fatigue in rheumatoid arthritis was an observational study which showed that 40% of the explained variance in fatigue could be accounted for by a combination of disease related factors; pain was demonstrated to be the single most important variable, accounting for 20% of this explained variance (Belza *et al.* 1993). This association was subsequently upheld in a large observational study (n=628), which also emphasised that pain along with other disease related factors, and moreover, not inflammation, were reported as the likely cause of fatigue (Wolfe *et al.* 1996). Further, pain severity also appears to influence the fatigue experience. A strong relationship (r=0.8) was shown between pain and fatigue intensities, in a cross-sectional study which had pain and fatigue as the primary outcomes; participants were patients with rheumatoid arthritis without fibromyalgia, and on stable does of synthetic disease modifying drugs (Mengshoel 1993). Two observational studies have reaffirmed the association between fatigue, and greater or higher pain levels (Belza 1995; Minnock and Bresnihan 2008); the more recent, a 2-year follow-up study, showed fatigue to be related to poor pain outcome A weakness in this study however, was that fatigue was only measured at follow-up (Minnock and Bresnihan 2008). Variability in fatigue was the primary outcome of a postal study in which patients with 3 distinct diagnoses, (rheumatoid arthritis, osteoarthritis and fibromyalgia), used up to 32 daily diaries to assess illness symptoms.

Daily pain was shown to be associated with increased fatigue in all groups, particularly in patients with rheumatoid arthritis along with fibromyalgia. Moreover, it was demonstrated that higher than average daily pain predicted elevated fatigue levels on the following day (β = 0.8, *SE* = 0.02, *t*(6753), $p<0.01$) in the combined diagnostic groups (Zautra *et al.* 2007). Another study highlighted the multidimensional nature of fatigue. In this cross sectional evaluation of health related quality of life pain was more strongly related to general fatigue (r =-0.592), and physical fatigue (r= 0.613, $p \leq -0.6$) as opposed to mental fatigue (r= -0.229) (Rupp *et al.* 2004). Further, when studied longitudinally, falls in fatigue levels following 3-months, and 6-months treatment with either traditional synthetic or newer biologic disease modifying drugs, respectively, was linked more to improvement in pain levels than in disease activity status (Pollard *et al.* 2006). Most studies support the contention that pain is an important contributor to the fatigue experience, its dominance as a symptom necessitates its inclusion in all studies examining contributory factors to fatigue.

In patients with psoriatic arthritis, findings in relations to the associations between fatigue and pain reflects those from cross-sectional analyses of patients with rheumatoid arthritis (Huyser *et al.* 1998). Only one longitudinal study to date, with fatigue as a primary outcome, has confirmed this relationship between fatigue and pain (β = 0.103, *SE* = 0.01, *t* (-18.4), $p < 0.0001$), in patients with psoriatic arthritis (Husted *et al.* 2009).

While the interrelationship between these two important patient' reported symptoms in both rheumatoid arthritis and psoriatic arthritis has been demonstrated, further longitudinal study of the dynamic between fatigue and pain, with fatigue as a primary outcome, is required exclusively in populations with inflammatory arthritis, in order to identify appropriate treatment strategies for fatigue prevention and management.

The link between fatigue and patient reported disability, demonstrated in both rheumatoid arthritis and psoriatic arthritis patients, is proposed as another contributory factor to the fatigue experience (Belza *et al.* 1993; Belza 1995; Wolfe and Michaud 2004; Mancuso *et al.* 2006; Repping-Wuts *et al.* 2007; Husted *et al.* 2009). One cross-sectional study showed that fatigue correlated with both functional status and activity among the elderly (Belza 1995). Qualitative evaluation confirmed that fatigue impedes mobility and activity (Nikolaus *et al.* 2010b). Patients with rheumatoid arthritis believe that having to work

harder and longer because of disability and the need to expend more energy to overcome functional limitation secondary to joint damage contributes to their fatigue (Hewlett *et al.* 2005b). This belief has been validated in a one year follow-up study which demonstrated that the HAQ-disability index at baseline was predictive of persistent severe fatigue at follow-up (OR = 2.8) (Repping-Wuts *et al.* 2007). However, a limitation of this study is that it only included patients with low-moderate levels of disease activity, and pain was not included as an outcome. Further evaluation of the interrelationship between fatigue and function, in patients during different phases of disease activity are indicated, where fatigue is measured alongside the traditional core outcome measures.

Sleep disturbance or poor quality sleep are recognised consequences of many rheumatic conditions (Belza 1995; Wolfe *et al.* 1996; Stone *et al.* 1997; Zautra *et al.* 2007). Pain and inflammation are recognised mediators of daytime sleepiness and fatigue in inflammatory rheumatic diseases (Lashley 2003; Smith and Wegener 2006). Patients with rheumatoid arthritis attribute 25-42% of sleep disturbance to the consequences of the disease process; chief culprits include disease activity, pain and mood (Drewes *et al.* 1998; Carr *et al.* 2003; Wolfe *et al.* 2006). It is not surprising therefore that sleep was also highlighted as an outcome of importance to patients through the patient perspective movement at OMERACT. As a consequence work in evaluating sleep quality in patients with rheumatoid arthritis is ongoing (Wells *et al.* 2009). Studies which evaluate sleep quality which have fatigue as a primary outcome are indicated at this time when interventions to improve fatigue outcome are been sought.

3.9.1 Non-disease related factors as the causal pathway to fatigue

Psychosocial factors

The influence of non-disease related factors on the fatigue experience is also important. Psychological and social factors, independent of diagnosis and disease status in inflammatory arthritis, are frequently proposed as contributory factors to fatigue. Those most frequently studied include affective disorders which encompass depressive mood and

anxiety, and psychosocial factors which encompass social stress and social support, as well as coping and the concept of self-efficacy.

It is difficult to disentangle the predictive or explanatory role played by depression and anxiety in the experience of fatigue in inflammatory arthritis; traditionally most studies have focused on patients' experience of pain more than fatigue. Early cross sectional studies demonstrated a moderately strong relationship between fatigue and depression, (r = 0.51) (Huyser *et al.* 1998); (r = 0.501), (Wolfe *et al.* 1996); (r = 0.440- 0.576), (Rupp *et al.* 2004), and fatigue and anxiety (r = 0.523), (Wolfe *et al.* 1996). However, in another this positive relationship between fatigue and depression was seen in both the study group (r=0.47), and also in the healthy control group (r=0.46), even though fatigue levels were lower in the latter (Belza 1995).

Independent of depression, anxiety has been shown to be related to fatigue (r = 0.38) (Mancuso *et al.* 2006). This was further demonstrated in a large (n=415) 7-year longitudinal study which found that throughout the study duration fatigue levels among patients with rheumatoid arthritis coupled with an affective disorder, were 10% greater than in patients with an affective disorder alone (Fifield *et al.* 2001). However, there are also studies which have failed to confirm the association between fatigue and mood in this disease group (Mancuso *et al.* 2006; Treharne *et al.* 2008). While another suggests no inter-relationship between the four variables (fatigue, pain, depression, anxiety) (Smedstad *et al.* 1996). Difficulty in clarifying the directional relationship between fatigue and mood states is hampered by the limited number of studies which had fatigue as a primary outcome; other restrictions include the lack of consensus on a standardised assessment tool for fatigue, a predominance of cross sectional as opposed to longitudinal studies, as well as a lack of follow-up and comparative studies. Further longitudinal studies with fatigue as a primary outcome measure using validated scales are required in the process of unravelling the interrelationship between fatigue and mood related disorders in patients with inflammatory arthritis.

The role of social support and social stress in the fatigue experience in rheumatoid arthritis are also reported. One longitudinal study showed that less social support and more social stress contributed to more fatigue (Mancuso *et al.* 2006); a similar but weaker effect was

seen in the control group. A cross sectional study showed that poor quality social support correlated with increased fatigue levels (Riemsma *et al.* 1998). Further, a lack of current social support coupled with an increase in social stress was shown to compound the degree of fatigue experienced (Huyser *et al.* 1998). These latter findings support those found on qualitative study a decade previous (Tack 1990a). A more recent study found stimulated production of the inflammatory cytokine IL-6 in the presence of social stress, to be associated with greater levels of self-reported fatigue (Davis *et al.* 2008). Despite different study designs the concordant results suggest that contributory factors to fatigue are not only clinical but also social in nature.

Longitudinal examination of the impact of coping strategies on outcome in patients with rheumatoid arthritis showed the maladaptive behaviour of avoidant coping to be related to more tiredness (Scharloo *et al.* 1999). While in a panel study (n = 446) perceived coping efficacy for fatigue was found to be lower, the higher the fatigue level experienced, indicating that patients with rheumatoid arthritis felt less equipped to cope with this symptom as opposed to others (Katz 1998). Furthermore, a single time point study on patients who believed they could cope with their fatigue (those with higher self-efficacy), demonstrated less fatigue, and those patients with high self-efficacy towards enlisting social networks also had less fatigue (Riemsma *et al.* 1998).

The effect of self-efficacy on the fatigue experience in rheumatoid arthritis has also been examined. The benefits of self-efficacy (perceived personal control) to disease outcomes, particularly the patient reported outcomes of pain and fatigue, have been demonstrated in cross-sectional and longitudinal studies, (Riemsma *et al.* 1998; Brekke *et al.* 2001), respectively, and in one randomised controlled trial of cognitive therapy (Evers *et al.* 2002). In another study self-efficacy was shown to be strongly related to fatigue both currently and prospectively, however follow-up was limited to 1-year (Treharne *et al.* 2008). Over a longer duration of 2-years the potential to modify self-efficacy in order to improve fatigue outcome was highlighted on observational study of registry data (n= 1,600). This study demonstrated a fatigue score (visual analogue scale 0-100) decline of 0.22, and a vitality score (Short Form -36 vitality score 0-100) increase of 0.20, for each corresponding unit increase in the baseline self-efficacy score (Brekke *et al.* 2001). In the

search for modifiable factors to improve fatigue outcome self-efficacy as a mediating variable warrants inclusion in studies in patients with inflammatory arthritis.

In summary, there is evidence that psychosocial supports (e.g. self-efficacy skills) can reduce, and psychosocial stressors (e.g. negative mood and relationships) can compound the burden of fatigue. This evidence is supported by a variety of studies with different methodological qualities. One major limitation to comparison is the lack of a standardised approach to measuring fatigue and use of a variety of fatigue scales with limited or no validation for use in patients with rheumatoid arthritis (Hewlett *et al.* 2007). Furthermore, studies reported bivariate as opposed to multivariate associations which limit interpretation when potential contributing factors to fatigue are multiple. Although direct comparison is difficult all studies agree on the direction of the relationship between the fatigue experience, and positive social resources and self-efficacy. Inclusion of these key contributing factors in prospective fatigue studies will serve to clarify understanding, and the scope for improvement of management strategies.

Demographics and patient characteristics

More generic factors including gender, disease duration, and physical de-conditioning are also proposed as contributing factors to fatigue. Whether demographics and physical conditioning contribute to fatigue in inflammatory arthritis is uncertain. Higher fatigue levels in females with rheumatoid arthritis were found in only previous cross-sectional studies (Belza *et al.* 1993; Huyser *et al.* 1998) and not in others, or in any longitudinal evaluation (Hewlett *et al.* 2008). So too was the case in patients with psoriatic arthritis with one single point study showing the female gender association (Husted *et al.* 2009), which was not upheld on longitudinal analysis (Husted *et al.* 2010). This might be attributed to female dominated samples as a consequence of convenience sampling for single time point studies. In patients with rheumatoid arthritis higher fatigue levels have been demonstrated among those most recently diagnosed and those with longer established disease (Belza *et al.* 1993; Huyser *et al.* 1998; Barlow *et al.* 1999). Decreased physical activity is another factor shown to contribute to fatigue on cross sectional analysis (Belza *et al.* 1993), while qualitative findings suggest that fatigue reduces a patient's capacity to engage in regular exercise (Hewlett *et al.* 2005b).

In keeping with the delineated research agenda for fatigue (Section 1.1), this section focused on the literature related to the inter-relationship between fatigue and other outcomes of the disease process, more than on factors which potentially influence disease pathogenesis, such as socio-demographics. An overview is provided of the principal independent variables (outcomes) of interest, namely, pain, disability, sleep, mood, and self-efficacy for coping with arthritis. It is reasonable to conclude that the exact nature of their relationship with the dependent variable of interest, fatigue in patients with inflammatory arthritis, is suitable for further examination and exploration. The next and final section of pertinent literature reviewed looks at the many consequences of this patient reported symptom.

3.9.2 Impact of fatigue

The importance of fatigue as an outcome in health care research is validated by studies which have highlighted its impact in patients with rheumatoid arthritis. Fatigue, next to pain is one of the most common patient reported symptoms of inflammatory arthritis and its consequences have been shown to affect many aspects of living (Tack 1990a; Hewlett *et al.* 2008; Rasker 2009). Apart from the previously mentioned impact on functional ability and performance, fatigue negatively influences occupational and rehabilitative activities, participation in social activities and so overall quality of life.

The clinical importance of fatigue is highlighted by the evidence of its negative impact on work status (Wolfe *et al.* 1996); the presence of fatigue was shown to be strongly associated with decreased work capacity, a strong predictor of work dysfunction, as well as of overall health status. It was demonstrated that a patient with a high fatigue score was six times more likely to report being unable to work and five times more likely to report only fair or poor health status (Wolfe *et al.* 1996). Qualitative evaluation confirmed that fatigue has the ability to reduce work, leisure and household activities to a minimum (Hewlett *et al.* 2005b).

Patients have also reported an emotional toll on relationships on account of fatigue, which further contributes to frustration, irritability and loss of control, feelings of resentment and

low self esteem, and uselessness (Hewlett *et al.* 2005b; Nikolaus *et al.* 2010b). The negative effect encroaches family activities and social networks (such as being unable to play with or care for grandchildren), work opportunities (a quarter having to restrict or change work hours), and sporting activities (half of the respondents had to give up their favourite sporting activity) (Repping-Wuts *et al.* 2008a).

The European Research on Incapacitating Diseases and Social Support (EURIDISS) profiles of patients (n=573) with early rheumatoid arthritis found that the quality of life over a 2-3 year period, in those experiencing much fatigue, declined the most, and that fatigue above tender joint count and pain, best distinguished quality of life profiles (Suurmeijer *et al.* 2001). Qualitative exploration of the consequence of fatigue has shown its impact permeates every sphere of life (Hewlett *et al.* 2005b). Overall it contributes to a sedentary lifestyle, and reduces quality of life (Belza 1994; Wolfe *et al.* 1996; Suurmeijer *et al.* 2001; Hewlett *et al.* 2005b; Repping-Wuts *et al.* 2008a).

These studies highlight the negative effect of fatigue on health care outcomes and quality of life. Moreover, they emphasise the need for health care providers to proactively implement evidence based management strategies to minimise the burden of this enduring symptom.

3.9.3 Approaches to the management of fatigue

The limited literature available on approaches to the management of fatigue in inflammatory arthritis can be divided into pharmacological and non pharmacological; non-pharmacological approaches can be again subdivided into non-complex education and self-management interventions, and more complex psychosocial interventions. Pharmacological approaches are first reviewed. As already discussed pharmacological interventions with fatigue as a primary outcome in inflammatory arthritis are only a relatively recent phenomenon, spurred by unsolicited patient reports of improvement in fatigue levels when treated with TNFi therapy (Weinblatt *et al.* 2003; Wolfe and Michaud 2004; Moreland *et al.* 2006). For this reason, despite the long standing nature of the traditional disease modifying medications, very little data exist on their effect on fatigue as a primary outcome (Pollard *et al.* 2006), explained by the fact that fatigue was not evaluated in most trial

published over the last decade (Felson *et al.* 2011b). Only randomised controlled trial in this area compared the gold standard medication methotrexate and the relatively newer synthetic drug leflunomide; this showed that both drugs improved fatigue levels measured as part of the Medical Outcomes Study Short Form (SF-36) energy and vitality scores (Strand *et al.* 2005). However, patients prescribed these medications still reported problematic fatigue which fuels the debate on whether or not persistent fatigue is due to disease activity, pain, global health, or a complex array of psychosocial variables (Pollard *et al.* 2006; Rasker 2009).

Non-pharmacological and non-complex approaches advocated in the management of patient reported symptoms of rheumatoid arthritis, such as pain and fatigue, include disease specific patient education and generic self-management strategies such as problem solving and goal setting (Lorig *et al.* 2004; Lorig *et al.* 2005). Because professional support for the management of fatigue is not widely available (Hewlett *et al.* 2005b; Repping-Wuts *et al.* 2008a), it is not surprising that the role of patient education as a self-management strategy for fatigue has not been evaluated to date. One randomised control trial of a formal UK Arthritis Self-Management programme for participants with generic arthritis showed a trend towards a reduction in fatigue at 4 months, and a significant reduction at 12 months (Barlow *et al.* 2000). Qualitative studies have reported on the limited success experienced by patients who practiced self-management strategies such as positive attitude, pacing and rest (Tack 1990a; Hewlett *et al.* 2005b; Repping-Wuts *et al.* 2008a). The role of these non-complex approaches to the management of fatigue in inflammatory arthritis, including patient education and self-management strategies, requires further exploration and evaluation.

Varying success is reported also from the limited reports on more complex interventions for the management of fatigue in inflammatory arthritis. One randomised controlled trial of cognitive behavioural therapy conducted among patients with rheumatoid arthritis of less than 8 years duration showed a significant improvement in fatigue, which was maintained 6-months post treatment (Evers *et al.* 2002). More recently, a randomised controlled trial tested cognitive behavioural techniques for self-management of fatigue in patients with rheumatoid arthritis. At the end of the six weeks the treatment group showed statistically

better scores than the control group for all measures of fatigue and well-being, furthermore this was maintained at 3-months follow-up assessment (Hewlett *et al.* 2011a).

Specific exercise programmes that target fatigue could also be regarded as more complex interventions. One-quasi-experimental study demonstrated benefits of regular and appropriate exercise in reducing the burden of fatigue in rheumatoid arthritis without the risk of exacerbation of other symptoms (Neuberger *et al.* 1997), and a large descriptive study (n=435) found that less fatigue was reported by exercisers versus non exercisers with rheumatoid arthritis (Lee *et al.* 2006). More recently in a randomised controlled intervention it was shown that while fatigue exerted a negative influence on exercise participation the symptom improved with regular exercise (Neuberger *et al.* 2007). Non-pharmaceutical interventions such as dynamic exercises, occupational therapy, and hydrotherapy are recommended as adjuncts to pharmaceutical interventions for patients with inflammatory arthritis (Combe *et al.* 2007). However, further evidence on best approaches to delivery of these interventions so as to positively impact on fatigue outcome is required.

To summarise, the management of fatigue has not been given a priority by professionals caring for patients with inflammatory arthritis (Repping-Wuts *et al.* 2008b). Patient self-management strategies include behavioural, cognitive and social means and are deemed by patients themselves to bring limited symptomatic relief (Hewlett *et al.* 2005b; Hewlett *et al.* 2008; Repping-Wuts *et al.* 2008a). Scientific evidence from formal robust studies on pharmacological, and non pharmacological interventions is scant (Felson *et al.* 2011a; Felson *et al.* 2011b), as the inclusion of fatigue as a standard outcome measure has only been relatively recently endorsed by the international rheumatology research community. The need for the development and validation of appropriate measurement scales for fatigue is both recognised and ongoing in order to improve measurement of this complex phenomenon in both rheumatoid arthritis (Hewlett *et al.* 2007; Minnock *et al.* 2009; Nicklin *et al.* 2010a; Nicklin *et al.* 2010b) and psoriatic arthritis (Chandran *et al.* 2007; Minnock *et al.* 2010), and to facilitate comparison of study findings. However, one of the many challenges to the measurement of this patient reported symptom is its multidimensional nature which will be next discussed.

3.10 The multidimensional nature of the symptom fatigue

Based on quantitative and qualitative evidence, consensus exists on the multi-dimensional nature of fatigue in rheumatoid arthritis (Tack 1990b; Wolfe *et al.* 1996; Hewlett *et al.* 2005b; Mease *et al.* 2005a; Repping-Wuts *et al.* 2008a). A dimension refers to a single component of a complex phenomenon (Polit and Hungler 1995). Similar to other concepts, fatigue in inflammatory arthritis, is defined and described by a variety of dimensions, often used interchangeably, and the disentanglement and interpretation of these dimensions can differ between individual theorists (Tiesinga *et al.* 1996). The variety of dimensions referred to within the generic literature on fatigue in chronic diseases include: physiological dimension (e.g. increased levels of pain and or inflammation, disturbed sleep), psychological dimension (e.g. depressive symptoms, daily stressors, anxiety), social dimension (e.g. poor social support, multiple social roles), personal factors (e.g. low self-efficacy, physical conditioning, lifestyle), cognitive factors (e.g. motivation) (Tack 1990b; Tiesinga *et al.* 1996; Huyser *et al.* 1998; Riemsma *et al.* 1998; Hewlett *et al.* 2005b).

The majority of these dimensions in patients with inflammatory arthritis have been presented earlier. In the context of this study topic on a patient reported outcome in chronic disease, the dimension of perception or subjectivity is significant (Piper *et al.* 1987). A subjective symptom is something apparent to the individual afflicted but not observable by others (The Free Dictionary 2010). Applied to the symptom of fatigue this acknowledges that fatigue cannot always be explained objectively (Tiesinga *et al.* 1996). For this reason both quantitative and qualitative studies are required in order to gain further understanding of this complex phenomenon in inflammatory arthritis (Tack 1990a, 1990b; Hewlett *et al.* 2005b; Repping-Wuts *et al.* 2008a), and provide an evidence base for the development of effective interventions. The subjective dimension of fatigue focuses on multiple self-reported components, chiefly, 1) temporal/ timing, 2) severity/intensity, 3) coping/evaluative 4) effect/impact 5) pattern/explicability (Tack 1990a, 1990b; Tiesinga *et al.* 1996; Hewlett *et al.* 2005b; Repping-Wuts *et al.* 2008a). These subjective components have been utilised to develop patient reported outcome measures (PROMS) for the purpose of evaluation and measurement of this complex concept in patients with rheumatoid arthritis (Tack 1990a; Nicklin *et al.* 2010b). It is precisely because exploration of patients'

perceptions gives insight into the experience, and impact of, this common and unpleasant symptom in inflammatory arthritis that it been given priority among nurse researchers (Tack 1990b; Hewlett *et al.* 2005b; Minnock and Bresnihan 2008; Repping-Wuts *et al.* 2008a; Minnock *et al.* 2009; Minnock *et al.* 2010). Knowledge gained and theoretical perspectives proposed from such exploratory work contribute to the growth of management strategies for the phenomenon of interest, namely, fatigue in inflammatory arthritis.

3.10.1 Literature Summary and Research Justification

Achieving optimal health status outcome for patients with inflammatory arthritis is the goal of modern healthcare (Smolen *et al.* 2010a). Although the precise pathogenesis of inflammatory arthritis remains unclear treatment of both the articular consequences and systemic clinical manifestations is far superior to previous decades. This is due to a combination of traditional and novel pharmacological approaches as well as judicious practice guided by evidence based treatment guidelines (Kavanaugh and Ritchlin 2006; Combe *et al.* 2007). For this reason regular patient monitoring, which includes patient reported outcome measures, is recommended as part of a strategy for achieving optimal outcome and best care (Smolen *et al.* 2010a). Great emphasis is being placed on incorporating outcomes important to patients for frequent measurement in clinical trials or clinical practice. Moreover, the fatigue research agenda highlights the need for studies focusing on clarification of the nature of the relationship between the patient' reported outcome fatigue, and other outcomes of the disease process.

While the literature confirms the fatigue assessment will aid understanding and, consequently, treatment and management of this symptom of inflammatory arthritis (Gladman *et al.* 2007b; Kirwan *et al.* 2007; Aletaha *et al.* 2008), moreover, it highlights the dearth in published clinical studies which have included fatigue as a primary outcome over the last decade (Felson *et al.* 2011a; Felson *et al.* 2011b). Furthermore, for fatigue to be validated as a core outcome then further study on the standardisation of assessment is required; this will permit direct study comparison between populations (Kirwan *et al.* 2007).

The rational development of appropriate therapeutic interventions to treat and promote self-care and professional management of fatigue is contingent on clarification of the contributory factors to fatigue. However, to date there is a lack of data from longitudinal observational studies so causation cannot be determined. In order to determine if fatigue is an independent attribute of the inflammatory response then study populations need to be confined to those with inflammatory arthritis only. Moreover, limitations identified in observational studies of including patients with only mild to moderately active disease (Repping-Wuts *et al.* 2007), and excluding populations from biologic registers on the basis of disease severity (Bergman *et al.* 2009) highlights a further knowledge gap in the literature. In the context of modern biologic disease modifying therapies longitudinal studies are required in both patients with inflammatory arthritis in order to determine the relationship between fatigue and the conventional measure of disease outcome. Moreover, comparative study of key potential contributory factors (pain, sleep, self-efficacy, mood, helplessness) in patients with minimal fatigue and those with persistent fatigue following TNFi therapy has not previously been undertaken.

Only four qualitative studies, published to date, serve to identify the knowledge gap in relation to patients' experience of fatigue in rheumatoid arthritis. Neither disease state nor treatment regimens were a consideration in the recruitment of participants to the previous four qualitative studies. Moreover, evidence from qualitative studies on the impact of modern pharmacological therapies, namely TNFi therapy, highlights their positive benefit to overall disease state and outcome (Edwards 2004; Marshall *et al.* 2004). Levels of fatigue experienced by patients at the time of interviews were only considered in one qualitative study (Hewlett *et al.* 2005b). Therefore, the nature and consequence of persistent high levels of fatigue, from the perspective of those with the disease, remains under-explored. Evaluation of persistent fatigue levels despite a good disease response following treatment of active disease is suitable for in-depth exploration to add a fresh perspective on outcome in the context of the modern biologic TNFi therapy.

Chapter 4 Research Methodology and Data Collection Methods

4.1 Research Methodology

The purpose of this chapter is to introduce the appropriate research methodology to study the phenomenon of fatigue in patients with inflammatory arthritis. It explains why the strategy most suitable to fulfill the research purpose was a combination of both quantitative and qualitative approaches (Creswell 2009). The type of quantitative and qualitative studies undertaken to address the study objectives are detailed. According to the convention of mixed methods, specifics are provided on how both methodologies were combined in relation to time ordering, weighting, and mixing stages of the process (Hanson *et al.* 2005; Creswell 2009; Doyle *et al.* 2009).

4.2 Research Purpose

To determine the clinical characteristics of, contributory factors to, and unexplained elements of fatigue in patients with inflammatory rheumatic diseases from the perspective of both the clinicians and the patients, and in so doing provide a basis for effective interventions. The research purpose was addressed through five objectives which aimed to:

I. quantify levels of fatigue in patients with two different inflammatory rheumatic diseases-
II. compare the properties of a one-dimensional and a multidimensional fatigue scale-
III. define the clinical characteristics of, and the relationship between fatigue and the conventional core set outcome measures-
IV. elucidate the elements of fatigue not explained by the core set outcome measures-
V. identify, from the literature, and from patients' experiences, potential modifiable factors to improve fatigue outcome.

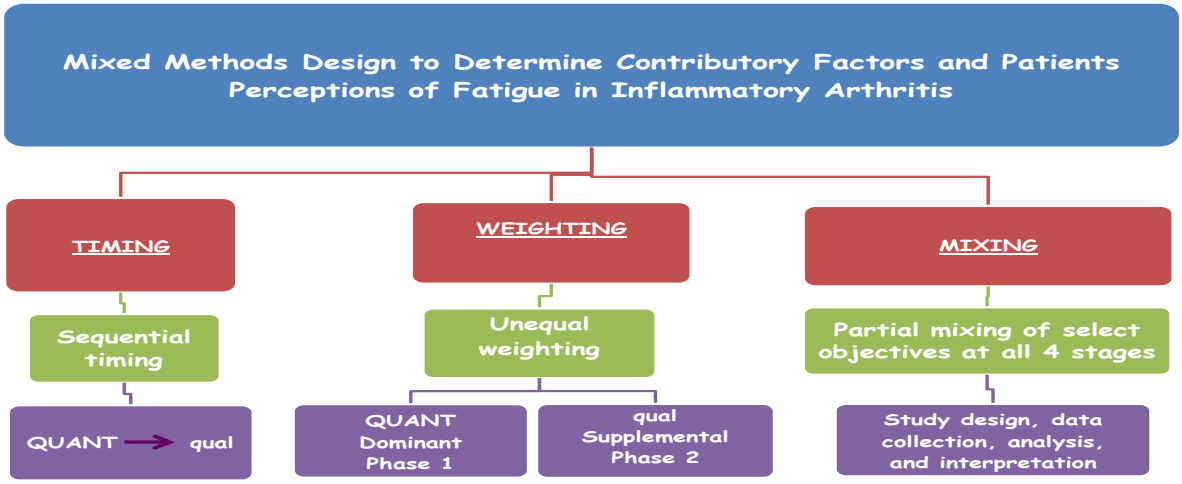
4.3 Study Title, Design and Types

The design appropriate to this study was the sequential explanatory design (Creswell 2009), as represented in (Figure 4-3). The initial dominant quantitative phase addressed the first four objectives in two separate components. The second qualitative phase addressed the fourth and fifth objectives. The mixed methods approach supported the use of a supplemental research strategy (qualitative) to collect narrative data that would not have been obtained if data collection were confined to the main quantitative (numeric) data (Morse 2003).

4.4 Timing, Weighting, Mixing of Methods

A mixed methods design decision tree (Creswell and Plano Clark 2007) was used to guide key decisions and choices in relation to i) time ordering of the quantitative and qualitative stages, ii) the relative weighting or priority given to the different methods and, iii) where the mixing and integration occurred (Figure 2-1). Moreover, the design was determined by the original research purpose. The origins of the topic of fatigue within outcome measurement research dictated the dominance of the quantitative strategy of inquiry and the deductive theoretical drive for this study (Morse *et al.* 2006).

Figure 4-1: Study design decision tree



Thee abbreviation of QUAN and qual represent the quantitative and qualitative stages of a mixed methods design (Morse 1991). This procedural notation uses upper and lower case to indicate the dominant quantitative weighting and the non-dominant qualitative weighting or higher priority of the methods, respectively, in the stages of this study (Leech and Onwegbuzie 2009). The arrow indicates that the data were collected sequentially (Hanson *et al.* 2005).

(Morse 1991; Hanson *et al.* 2005; Leech and Onwuegbuzie 2009)

Mixing/Integration

Integration refers to the stages within the research process where mixing of the quantitative and qualitative methods occurred (Tashakkori and Teddlie 1998; Creswell and Plano Clark 2007). In this study partial mixing of methods occurred throughout all stages of the research design. It commenced at the setting of the research objectives, it continued as data analysis from the first longitudinal quantitative study determined participant selection for both the second quantitative comparative component of study, and for the qualitative descriptive study; data were integrated during the narrative and inference phase (Doyle *et al.* 2009; Leech and Onwuegbuzie 2009). As the dominant phase of the study was quantitative this determined that the overall theoretical drive of this mixed methods study was deductive: findings from the supplemental, qualitative, inductive phase 2 were integrated with those of the dominant first phase during the discussion (Morse *et al.* 2006).

4.5 Methods of Data collection: Introduction

This second section of the methodology chapter presents the phases and procedures used throughout the study: i) population, sampling and participants, ii) data collection methods and plan, iii) study procedures and the permission process, iv) analytical procedures and methods (Figure 4-3). In keeping with the mixed methods study design the research methods for the two components of the dominant quantitative data collection phase will be discussed first. Lastly, the methods employed in the supplemental qualitative second phase of data collection are presented.

4.6 Prospective, Longitudinal, Quantitative, Descriptive Study of Fatigue Levels and Characteristics in Inflammatory Arthritis

4.6.1 Population, sampling, participants

The study was undertaken in an Academic Medical Centre rheumatology department which has a national and international reputation in clinical, basic and translational research. At

the time this study was conducted over 5,000 patients with a musculoskeletal condition were reviewed annually within the department; approximately 900 of these patients were first time referrals for diagnosis. The ratio of patients with inflammatory arthritis to those with another musculoskeletal disorder is estimated at 1:3.

The target population was patients with a diagnosis of inflammatory arthritis commencing disease modifying anti-rheumatic drugs, namely, anti-tumour necrosing factor α (TNFi) therapy, for the pharmacological management of their active disease state. At the time the study was planned the average number of patients commenced on a TNFi therapy was 12.5 patients per month. Eligible patients recruited to participate were those with a diagnosis of rheumatoid arthritis (n≈1400), or psoriatic arthritis (n≈350), and moderate to high levels of disease activity, according to the DAS28 (http://www.das-score.nl ; van Riel 1992), and therefore the greatest potential for change in disease outcome.

Inclusion criteria were: -

i) Consenting male or female patients aged 18 years or more,
ii) Confirmed American College of Rheumatology (ACR) (formerly the American Rheumatism Association) diagnostic criteria for rheumatoid arthritis (Appendix 7) (Arnett *et al.* 1988), and recognised diagnostic criteria for psoriatic arthritis (Moll and Wright 1973b; Taylor *et al.* 2006) (Appendix 3).
iii) Newly prescribed TNFi biologic therapy for their current active disease status that is DAS28 ≥3.2.

Exclusion criteria were: -

i) Patients were excluded from the study if they had a primary diagnosis of fibromyalgia syndrome or chronic fatigue syndrome.

Consecutive sampling, of the total population of accessible and eligible patients who attended the study site for the first 18 months of the study, was undertaken (Polit and Beck 2010a). The 18 month recruitment period was considered sufficiently long to minimize sampling biases such as seasonal, or time related variations, so enhancing representativeness of the sample.

Sample size was determined by a previous pilot study which served as preparatory field-work. In the pilot study a 0-10 numeric rating scale used to measure fatigue indicated that the mean baseline fatigue level of patients with rheumatoid arthritis was 6.7 (SD ± 2.1). This decreased to 4.3 (SD ± 2.6) with improvement in disease status following pharmacological treatment (Minnock *et al.* 2009; Minnock *et al.* 2010). Assuming a decrease of at least 2 in the mean level of fatigue following treatment, with a standard deviation of 2.6, an alpha level of 0.05 (2-tailed test) and a power of 95%, this necessitated recruitment of a minimum of 38 to each diagnostic group. However, to support statistical analysis, such as multiple regressions analysis with seven independent variables, using the guideline of 50 cases minimum plus eight cases for each variable (Tabachnick and Fidell 2001), in the first phase of the study, as well as the selection of specific sub-groups for the second component of this quantitative phase, the recruitment target number was set at 90 patients with rheumatoid arthritis and the minimum 38 with psoriatic arthritis. The total population of eligible patients who attended the study site for the first 18 months of the study was included in order to allow for an attrition rate of 25%. Data collection continued for a further 6 months after enrolment of the last candidates in order to collect 3 and 6-month follow-up data, (12.5 x 18 months (+ 6 months follow-up) = 225-25% attrition =169 potential study participants over 2 years). Best practice recommends that drug therapy should be adjusted at least every 3-months until desired treatment target is reached (Smolen *et al.* 2010a). At least 150 patients with these diagnoses commence treatment each year. Therefore, realisation of this sample size and completion of the first longitudinal component of data collection within the projected 2–year period was feasible.

4.6.2 Data collection methods and plan

Data Collection Methods

Numeric data was extracted from: -

1) Routine clinical measures of disease activity, namely the American College of Rheumatology (ACR) core set of outcome measures, and
2) Two additional scales chosen to measure fatigue, included specifically for the purpose of the study. These will now be described in turn.

4.7 Clinical Measures: ACR Core Set Outcome Measures

The clinical assessment of disease activity was undertaken using six of the internationally agreed ACR core set of outcomes measures which can be reported individually (Felson *et al.* 1993). These can also be reported as part of an index of disease activity, the disease activity score (DAS) (van Gestel and Stucki 1999), and of the EULAR response criteria (van Gestel *et al.* 1999). These will now be described, a) individually and, b) as part of both the disease activity score, and c) of the EULAR Response Criteria.

ACR Core Set Outcome Measures

These six measures can be sub-divided into objective, clinician derived, clinical outcome measures, and subjective patient reported outcome measures. The objective clinical measures, reflecting synovitis, recorded and used in this study were: -

1) 28-swollen joint count,
2) 28-tender joint count,
3) Laboratory measurement of an acute-phase reactant; C-reactive protein;

The subjective patient reported outcomes recorded and used in the study were: -

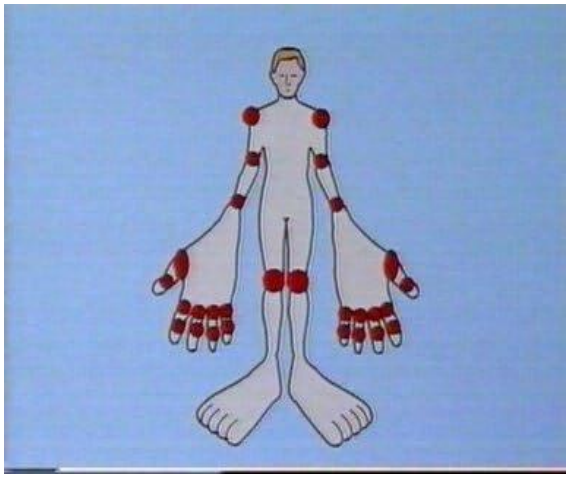
4) Patient assessment of joint pain on a 10 point numeric rating scale (NRS) (1-10),
5) Patient global assessment of disease activity on a 10 point numeric rating scale (1-10) (Appendix 10),
6) Patient assessment of function using the health assessment questionnaire disability index (HAQ) (Appendix 8).

28-Swollen Joint Count and 28-Tender Joint Count

All participants underwent serial measurement of swollen and tender joints using the 28 joint indices. In practice variable numbers of joint counts can be conducted and all have been shown to adequately detect differences between treatment and placebo in a patient with rheumatoid arthritis and psoriatic arthritis (Fuchs and Pincus 1994; Mease *et al.* 2005a; Mease *et al.* 2005b). However, the 28 swollen and tender joint count are easy to use and have been shown to be as valid as the more extensive counts (Prevoo *et al.* 1995). For

this reason it is most extensively used in clinical practice and the index of choice for this study (Figure 4-2). Swelling and tenderness were measured separately as they provide different information. Swelling has been shown to correlate with the objective biochemical measure of inflammation, the acute-phase reactant C-reactive protein. Tenderness has been shown to be more sensitive to change and to correlate with pain, a patient reported measure (van Riel and Scott 2004).

Figure 4-2: Identification of 28-joint count



20 small joints of hands:

-10 Proximal interphalangeal (PIP's),

-10 Metacarpophalangeal joints, MCP's),

2 wrists

2 elbows

2 shoulders

2 knees

Reproduced by kind permission of Prof Piet L.C.M. van Riel. (Appendix 9) Source taken from van Riel P.L.C.M. (2010) DAS_Score.NL Home of the DAS: Disease Activity Score in Rheumatoid Arthritis. http://www.das-score.nl/www.das-score.nl/. Nijmegen

The joints were scored for swelling on a 0-1 scale; 0=no swelling, 1=swelling and the individual joint scores were summed (range 0-28). In the same way, joints were scored for tenderness on a 0-1 scale; 0=no tenderness, 1=tenderness, and the individual joint scores were summed (range 0-28) (van Riel and Scott 2004). The information on swelling and tenderness was then recorded manually on a predesigned proforma.

Acute Phase Reactants: C - Reactive Protein

This biochemical blood test, C-reactive protein (CRP), is an acute-phase reactant, that is, a non specific measure of inflammation which reflects short term or recent change in disease activity. Normal concentration in healthy human serum is usually lower than 10 mg/L, local laboratory reference range was 0-30mg/L. It has been shown to correlate with other disease

activity variables and to be sensitive to change (van Leeuwen *et al.* 1993), in patients with rheumatoid arthritis.

The CRP has previously been shown to be less sensitive to change in patients with psoriatic arthritis (Gladman *et al.* 2005c). However, its use across both disease entities is widespread in clinical practice; therefore, its use for both diagnostic groups within this study was considered appropriate. This information was recorded manually on the biologic database.

The three other core set outcome measures captured were the patient reported outcomes: i) pain, ii) global health, and iii) functional activity, which were self-completed and documented on a predesigned proforma.

Patient Assessment of Joint Pain

Pain was measured using a 10 point horizontal numeric rating scale with anchors of 1 and 10, in accordance with the ACR recommendations (Felson *et al.* 1995a) (Appendix 6). Patients were asked to document on a proforma their answer to the question '*How much PAIN have you had over the past week?', and to 'circle the number that most closely indicated how much pain you had over the last week using the numeric rating scale from 1=none at all to 10 =a great deal'.* Numeric rating scales, regarded as primary variations of either Likert or visual analogue scale types (Bellamy *et al.* 1999), were the format used within the clinical setting because of their demonstrated ease of use and understanding for patients, and their higher reliability among illiterate patients (Ferraz *et al.* 1990; Williamson and Hoggart 2005).

The sensitivity to change of numeric rating scales in both rheumatoid arthritis and psoriatic arthritis has been demonstrated (Anderson and Chernoff 1993; Minnock *et al.* 2009; Minnock *et al.* 2010). Minimum clinically important difference for arthritis pain measured on a visual analogue scales was defined previously as approximately 10% improvement from baseline (Wells *et al.* 1993; Farrar *et al.* 2001; Wells *et al.* 2007; Dworkin *et al.* 2008; Pope *et al.* 2009).

Patient Global Health Assessment

Patient Global Health assessment is another agreed core outcome measure (Felson *et al.* 1995a). The global health term refers to a patient opinion scale which assesses either disease activity or general health depending on wording used (van der Heijde *et al.* 1993; Felson *et al.* 1995a; Sanderson and Kirwan 2009). In this study patient global health status was measured using a 10 point horizontal numeric rating scale to appraise disease activity (Appendix 6). The instruction to patients was '*Considering all the ways your arthritis affects you…circle the number that most closely indicates how active your arthritis has been over the last week'* using the numeric rating scale ranging from 1=not at all to 10=a great deal'. Minimum clinically important difference defined previously for patient global health status visual analogue scales are defined as approximately 10% improvement from baseline (Wells *et al.* 1993; Farrar *et al.* 2001; Wells *et al.* 2007; Dworkin *et al.* 2008; Pope *et al.* 2009).

Minimally important differences for pain and global health in patients with psoriatic arthritis on a visual analogue scale was determined previously to approximate a 10% change (Kwok and Pope 2010).

The Health Assessment Questionnaire Disability Index

Patient assessment of physical function is another core outcome measure (Felson *et al.* 1995a). The health assessment questionnaire (HAQ) disability index was the self-reported measure used to capture patients' level of function (Appendix 8). First introduced in 1980 (Fries *et al.* 1980), it was among the first patient-reported outcome measures initially designed to represent a model of patient-oriented outcome assessment (Bruce and Fries 2005). Although its origins are in the field of rheumatology it is regarded as a generic as opposed to a disease specific measure. The creation of the HAQ was based on 5 generic health outcome dimensions derived from patient-centred health value studies on what patients want, which were: 1) to avoid disability, 2) to be free of pain and discomfort, 3) to avoid adverse effects of treatment, 4) to keep medical costs low, and 5) to postpone death. The original full HAQ assesses all five dimensions. However, the version used in this study was the short or 2-page HAQ which captures disability only, known as the HAQ–Disability

Index (HAQ-DI), (without the HAQ's patient global and pain VAS, as these were captured as detailed previously). This is the most commonly used in clinical practice and in non-randomised controlled research studies (Bruce and Fries 2005; Kalyoncu *et al.* 2009). The HAQ-disability index measured patients' functional ability over the previous week by assessing upper and lower limb activities. A total of 20 questions cover eight categories of functioning (number of questions): dressing (2), rising (2), eating (3), walking (2), hygiene (3), reach (2), grip (3), and usual activities (3).

Each item is scored on a four-level difficulty scale from 0 to 3, representing normal (no difficulty) (0), some difficulty (1), much difficulty (2), and unable to do (3). The highest score in each category determines the score for the category, unless aids or devices are required. Where aids or devices or physical assistance are required a lower score increases to the level of 2, to more accurately represent underlying disability. The eight category scores are averaged into an overall HAQ-disability index on a scale from zero (no disability) to three (completely disabled). If less than six categories were completed by a patient the HAQ-disability index was not computed. The scale has 25 possible values, (8-24/8), so is not regarded as a truly continuous scale (i.e., 0, 0.125, 0.250, 0.375 … 3). Scores range from 0-3; scores of 0-1 represents mild to moderate functional difficulty, 1-2 represents moderate to severe disability and scores of 2-3 are indicative of severe to very severe disability (Bruce and Fries 2005). A change of between 0.10 and 0.22 from baseline represents a minimal clinically important difference in patients with rheumatoid arthritis (Wells *et al.* 1993; Bruce and Fries 2003b; Pope *et al.* 2009) .

The HAQ-disability index is self-explanatory and can be completed in five minutes approximately and with some practice can be quickly scored by clinicians in the clinical setting. The HAQ-disability index is copyrighted by Stanford University to ensure that it will not be modified in order to preserve the validity of its findings and contribute to standardisation of assessment across studies. However, it is considered to be in the public domain, free of charge, with the request that users cite relevant HAQ articles(s) in their publications (Bruce and Fries 2003b).

It has been extensively validated across a variety of diseases and conditions including rheumatoid arthritis and psoriatic arthritis (Bruce and Fries 2003a): construct validity and

sensitivity to change have been demonstrated in numerous observational studies and clinical trials (Bruce and Fries 2003b). It has been significantly correlated with health status measures used throughout this study, namely, the biochemical acute-phase reactant – CRP (Jansen *et al.* 2000; Combe *et al.* 2003), and clinical measures-swollen and tender joint counts (Ramey *et al.* 1992), as well as the self report Disease Activity Score (Combe *et al.* 2003), and the Beck Depression Scale (Sokka *et al.* 2000).

The minimal clinical important difference for HAQ-disability index in patients with psoriatic arthritis was found to be a change of 0.13 (Kwok and Pope 2010).

4.7.1 Indices derived from the ACR core set outcome measures

Both the Disease Activity Score 28 (DAS28) and the EULAR response criteria are indices derived from the ACR core set outcome measures. Both were utilised to determine change in disease activity status following treatment, and to categorise this degree of response, respectively. These will now be described.

Disease Activity Score 28

The Disease Activity Score 28 (DAS28) is a statistically derived composite index calculated using data from four core outcome measures: - i) 28-swollen joint count, ii) 28-tender joint count, iii) patient global assessment of disease activity and, iv) C-reactive protein; combined into a single measure (http://www.das-score.nl). This composite score permits comparability of disease activity between patients (van der Heijde *et al.* 1993; Prevoo *et al.* 1995). The DAS28 is regarded as the most useful single gold standard measure for assessment of disease activity in inflammatory arthritis in daily clinical practice (van Riel 2001). It has been shown to be as valid as disease activity scores that use more numerous and comprehensive joint scores (Prevoo *et al.* 1995). The advised time to completion is 3-5 minutes which explains its common use in clinical practice, and suitability for this study (Fransen *et al.* 2003). It has been shown to discriminate between patients with high and low disease activity and between treatment and placebo patient

groups in interventional studies (Wijnands *et al.* 1992). It is validated for use in patients with early and long standing inflammatory arthritis (Prevoo *et al.* 1995).

DAS28 is used extensively to measure patients' response to treatment particularly with the advent of new and expensive biologic therapies (Ledingham *et al.* 2005). The advantages of using the DAS28 in this study were that it provided, i) a continuous measure of disease activity over time and, ii) an absolute measure of disease state at a single time point. The DAS28 provided a number between 0 and 10, indicating how active the inflammatory arthritis is at that time point. A DAS28 above 5.1 indicated high disease activity whereas a DAS28 below 3.2 indicated low disease activity. Remission was indicated by a DAS28 lower than 2.6 (http://www.das-score.nl ; van Riel) (Table 4-1).

Table 4-1: Disease Activity Scale 28

	Thresholds of Disease Activity
DAS28 Range 0-10	**Remission < 2.6; 2.6 ≤ Low ≤ 3.2; 3.2 < Moderate ≤ 5.1; High > 5.1**

The original composite disease activity score was developed for use in patients with rheumatoid arthritis. However, it has since been shown to be discriminant and responsive when used to assess patients with psoriatic arthritis (Gladman *et al.* 2005c; Mease *et al.* 2005a) making it a suitable tool for use in this study with these two diagnostic groups.

In this study the DAS28 was used 6-months post baseline to categorise patients according to disease response. A subgroup of patients with good disease response 6 months post-baseline was identified within the sample.

EULAR Response Criteria

The EULAR response criteria are based on attained levels and change in DAS28. Through the calculation of both the change in disease activity as well as current disease activity patients were classified as good, moderate or non-responders (Table 4-2).

Table 4-2: EULAR Response Criteria

DAS28 Improvement	***> 1.2***	***> 0.6 - ≤ 1.2***	***< 0.6***
Present DAS28			
< 3.2	Good Response	Moderate Response	No Response
3.2 - 5.1	Moderate Response	Moderate Response	No Response
>5.1	Moderate Response	No Response	No Response

This DAS-based response criteria discriminate between treatments, and correlates with disease process and outcome variables (Fransen and van Riel 2005). Although originally developed for use in rheumatoid arthritis (van Gestel *et al.* 1996), its use in patients with psoriatic arthritis prescribed TNFi therapy has been reported from clinical trials (Antoni *et al.* 2005a; Kavanaugh and Fransen 2006). Moreover, it has also been shown to be both discriminant and responsive in longitudinal observational studies (Kristensen *et al.* 2008). Therefore it was considered suitable for use with both diagnostic groups in this study.

These validated DAS28-based criteria were used to measure individual response and improvement in disease activity status 6-months post-baseline (Wijnands *et al.* 1992; van der Heijde *et al.* 1993; van Gestel *et al.* 1996; van Gestel and Stucki 1997). This permitted the improvement or response in any one patient to be compared between two different time points as displayed in Table 4:2. To be classified as responders, patients demonstrated a significant reduction in DAS28 as well as a low current disease activity (Fransen and van Riel 2005). This was done at the end of the first quantitative component of study to identify participants for the second quantitative study, the comparative prospective study. Using the EULAR Response Criteria patients who demonstrated a moderate or good response in disease activity without a corresponding or parallel improvement in fatigue were identified for the comparative prospective study designed to meet the fourth objective in elucidating unique elements of fatigue.

4.7.2 Fatigue assessment: one-dimensional and multidimensional scales

A major objective of this study was to compare and contrast the measurement properties (psychometric) of a one-dimensional and a multidimensional fatigue scale. Fatigue was measured using two fatigue scales validated for use in rheumatoid arthritis: 1) a one-dimensional ordinal, verbal rating scale (VRS), and 2) a multidimensional assessment of fatigue scale (MAF) (Belza *et al.* 1993; Belza 1995). Key psychometric properties of instruments suitable for outcome measurement in clinical studies were examined across both scales. Measurement properties were compared in terms of their validity (truth), reliability and sensitivity (discrimination), and feasibility (Boers *et al.* 1998; Wolfe 2004) across the two disease groups. Therefore two levels of measurement were used in the assessment of fatigue: ordinal and interval scale data. The 5-points of the verbal rating scale provided data in rank order, with inexact distances between each point, known as ordinal data, and suitable to non-parametric analysis. The multidimensional scale provided data from ten point numeric rating scales; the interval between values is interpretable, therefore the data, known as interval data, is suitable for parametric analysis (Trochim 2006).

One-Dimensional Verbal Rating Scale

A 5-point verbal rating scale was used to quantify one dimension of fatigue at the 3-timepoints. The fatigue question focused on the dimension of severity as follows: *Fatigue severity over the past week? Please indicate your level of fatigue by choosing the word that closely matches your fatigue: None, Mild, Moderate, Severe, and Very Severe. Patients were asked to document their answer on the proforma* (Appendix 10). Ordinal scales are like Likert scales in that response categories have a rank order, but the intervals between values cannot be presumed equal (Jamieson 2004). Nonetheless, the ordinal fatigue scale was purposively chosen for this study on account of its ease of use in clinical practice; this was an important consideration in instrument choice (Wolfe 2004). The validity of fatigue measurement in descriptive studies in rheumatoid arthritis using ordinal scales with response options of ‘none’ to ‘very severe’ has been reported, however due to its limited nature further validation studies were recommended (Hewlett *et al.* 2007). Previous observational studies demonstrated content and construct validity through differentiating

between rheumatoid arthritis patients with and without inflammation, showing associations between fatigue and other symptoms, such as poor coping ability with fatigue, and poor sleep (Pinals *et al.* 1982; Stone *et al.* 1997; Katz 1998). Evidence to further validate the use of an ordinal fatigue verbal rating scale in the measurement of fatigue in patients with inflammatory arthritis, following and intervention, was sought.

Multidimensional Assessment of Fatigue Scale (MAF)

Fatigue was also measured using a multidimensional tool, the multidimensional assessment of fatigue scale (Multidimensional Assessment of Fatigue 1990) (Appendix 11). This scale was chosen because it was the only rheumatoid arthritis-specific scale available at the time of study design (Hewlett *et al.* 2007). The scale comprises 16 questions which measures four dimensions of fatigue, severity, distress, impact/interference, and timing, based on the past week. Questions 1-2 relate to severity: "To what degree have you experienced fatigue", (anchors "not at all", to "A great deal"); "How severe is the fatigue you have been experiencing", (anchors "Mild", and "Severe"). Question 3 measures distress, "To what degree has fatigue caused you distress", (anchors "No distress", to "A great deal of distress"). These items are scored on a 1-10 scale. Eleven questions, 4-14, measure "…to what degree has fatigue interfered with your ability to do the following activities"; activities include "household chores, cook, wash/bathe, dress, work, visit or socialise with friends or family, engage in sexual activity, engage in leisure and recreational activities, shop and do errands, walk, and exercise (other than walking)". These items are scored on a 1-10 scale, patients are asked to circle the number that mostly closely indicates how they have been feeling in relation to fatigue (Belza *et al.* 1993; Belza 1995). Each question on the multidimensional scales has an exclusion check box and instructions advise patients '*for activities you don't do, for reasons other than fatigue (e.g. you don't work because you are retired) check the box'*.

One question, 15, is a time-based measure of fatigue; "Over the past week, how often have you been fatigued?" Response options are categories of "Every day"; "Most days but not all days"; "Occasionally but not most days"; "Hardly any days". Items are scored 4, 3, 2, 1, and then multiplied by 2.5 to convert to a score ranging from 2.5-10. The final question, 16, measures change in fatigue "To what degree has your fatigue changed during the past

week?" "Increased"; "Stayed the same"; "Fatigue gone up and down"; "Decreased". This item is not included in any of the summary scales.

The total score is the sum of the 3 severity and distress questions 1-3 (range 1-30), plus the mean of the sum of questions 4-14 of the interference sub scale (range 1-10), plus the one time based question (15) (range 2.5-10). This yields a score which ranges from 1-50 which is referred to as the Global Fatigue Index (GFI) (GFI =∑ questions 1-3 + ∑n (questions 4-14) /n+question15). Question 16 is not included in the global fatigue index. Reported population norms for healthy individuals is approximately 16-17 (Belza 1995).

The scales multidimensional design has been confirmed by factor analysis, however, a limitation highlighted previously is that as the total score represents a combination of all the subscales the scale becomes unidimensional on reporting (Multidimensional Assessment of Fatigue 1990; Wolfe 2004). The multidimensional assessment of fatigue scale is regarded as easy to administer and score, it is relatively short in length, and it assesses the subjective aspects of fatigue such as quantity, degree, distress, impact, and timing. Permission to use the multidimensional assessment of fatigue scale was obtained from the author (Appendix 12).

The scale was developed from the oncology Piper Fatigue Scale which supports its face and content validity, while tests against other fatigue scales supported its criterion validity (Hewlett *et al.* 2007). A high Cronbach's alpha of 0.93 demonstrated its good internal consistency in studies of patients with rheumatoid arthritis (Belza *et al.* 1993; Belza 1995). Concurrent validity was previously confirmed (r = 0.84) against the fatigue subscale of the Profile of Mood States (Belza *et al.* 1993; Neuberger *et al.* 1997). Construct validity is evident through moderate convergence (0.78; $p < 0.001$) with disease activity measures, mood and sleep (Belza *et al.* 1993; Neuberger *et al.* 1997): divergence is documented where higher scores differentiate between patients with and without a history of depression (Belza 1995) between different levels of disease activity, and between patients and controls (Gerber *et al.* 2003; Jump *et al.* 2004). Therefore, there is reasonable evidence of its validation for measuring fatigue in rheumatoid arthritis (Hewlett *et al.* 2007).

Sensitivity to change of the multidimensional scale was demonstrated following drug and exercise intervention (Neuberger *et al.* 1997; Kaltwasser *et al.* 2001). Nonetheless, further evidence of the validation of this scale in rheumatoid arthritis patients was recommended particularly in relation to its sensitivity to change following an intervention (Hewlett *et al.* 2007). This study also examined fatigue levels in patients with different levels of disease activity.

The multidimensional assessment of fatigue scale has not been used previously in the assessment of fatigue in patients with psoriatic arthritis.

4.7.3 Data collection plan

Patients' recruited to this first longitudinal phase of study underwent standard clinical assessments of disease activity using the core set of outcome measures, with fatigue included as an additional assessment, at 3-time points: - baseline, 3-months, and 6-months. Assessments were undertaken by the members of the rheumatology clinical team as part of routine clinical care for this patient group. The relevant data was captured by the clinicians on the local biologic therapy database in real-time. Data captured consisted of two types. These were data extracted from routine measures in clinical practice using the core set outcome measures, and also data captured specifically for this study. Data captured specifically for the purpose of the study included all numeric data on fatigue from this quantitative longitudinal study. Disease activity was best monitored longitudinally through serial measurements as opposed to single point measurements. Serial measurements have been shown to predict disease outcome, as defined by radiographic progression and functional disability (Drossaers-Bakker *et al.* 2002). The value of serial data in this study was that they showed trends and temporal effects. This serial data on the study cohort was extracted electronically from the hospital data base for the purpose of this mixed methods study.

In order to enhance uniformity of clinical assessment the techniques employed were in accordance with recommended specific methods of assessing each disease activity measure of the core set (Appendix 6) (Felson *et al.* 1993; Scott *et al.* 1996). Skills training on

clinical assessment in inflammatory arthritis is undertaken twice yearly by clinicians (clinical nurse specialist and medical team) within the department to enhance inter-rater and intra-rater reliability (Walsh *et al.* 2008).

Patients were asked to complete the profroma containing the patient reported outcome measures in the waiting area following check-in. In order to enhance the quality of the data the questionnaires were checked for completeness by the clinicians during the clinical appointment. This thorough approach to data collection is inculcated within practice as outcome measurement is a major programme of translational research within the department. These data were subsequently entered into the local biologic database by a data manager. This custom built electronic data base is programmed to decline data outside the expected parameters as an inbuilt quality control mechanism for data entry.

4.7.4 Study procedure and permission process

The researcher presented the study detail and logistics to the key medical and nursing personnel within the department in order to prepare them for their key role in recruitment, and facilitation of informed consent by study participants. A letter of introduction, evidence of ethical approval, an abstract version of the study, and the researcher's contact details were made available to the gatekeepers, and appropriate line managers.

Clinical nurse specialists were the key gatekeepers who invited patients meeting the eligibility criteria to participate in the study. Patients satisfying the inclusion criteria were referred to the clinical nurse specialists for pre-treatment screening, education, and commencement of TNFi therapy as appropriate. During this pre-treatment interval the clinical nurse specialists informed the potential participants of the study verbally, and in writing using the specific participant information leaflet (Appendix 13). Information given included recruitment and data collection procedures, that no extra visits would be required for the first longitudinal study component, voluntary participation in the study, the right to withdraw without prejudice to care, assurance of confidentiality, potential benefits, no associated risk of harm, researcher's contact details and an offer to answer any questions. Patients had the 2 week screening interval to consider the study and when ready to

commence treatment they were then invited by the clinical nurse specialist to volunteer their participation in this study.

At this point it was reiterated to patients that the burden of participation in the initial longitudinal study was minimal. Participation involved the completion of the extra fatigue scales as patients ordinarily attend and complete the other clinical assessments of disease activity, at the 3 specified time points following commencement of their new drug therapy. It was also reiterated that only those patients who were identified as having persistent fatigue would be asked to volunteer participation in the subsequent comparative and qualitative studies. Those agreeing to participate were asked to sign the approved consent form (Appendix 14). The participant information portion was retained by the patient, and the signed and witnessed consent form was filed by the clinical nurse specialists. The clinical nurse specialists continued to recruit patients in this manner until sufficient numbers of patients with rheumatoid arthritis and with psoriatic arthritis were enrolled.

4.7.5 Analytical procedures and methods

The computer software package Microsoft Excel and the statistical package SPSS 16.0 for Windows (SPSS.com 2009) were used to analyse the data. Descriptive information (key demographics) was provided for the study sample of 130 patients for 2 to 3 separate clinic visits. Clinical assessments at each visit included the core set of outcome measures and the primary outcome was fatigue assessment using the verbal rating scale and the multidimensional assessment of fatigue scales. Summary measures used included frequency counts and measures of central tendency (mean/medians), and dispersion (standard deviations/interquartile ranges). Data were presented either numerically or graphically. Partial per protocol procedure was adopted therefore participants who were evaluated on at least two of the three timepoints were included. Missing data were not imputed; results tables report actual response rate and valid percentages.

DATA EXPLORATION

The fatigue and core set variables were first plotted to observe data distribution and then normality of distribution was tested using the Shapiro-Wilk test. All variables deviated from a normal distribution with the exception of DAS28 at baseline. Therefore, both mean and median values were presented and parametric and non parametric tests employed for statistical analysis, as appropriate. Historically, these clinical data have been analysed using parametric and non-parametric tests without any reference to data transformation (Pollard *et al.* 2006; Husted *et al.* 2010). To facilitate comparison of this study's results with previous studies, although data were skewed, the less robust non-parametric tests were used (Altman 1991, p. 145.)

COMPARING GROUPS AND POST HOC ANALYSIS- CONTINUOUS DATA

Although the data for the core set variable and the multidimensional fatigue scale were not normally distributed the parametric test within groups one-way ANOVA, which examines the difference between means of more than two treatment groups, was used to test the null hypothesis of equal treatment means between the clinical variables (core set outcomes and fatigue) at the 3 separate time points. It is generally held that ANOVA is not greatly influenced if the distribution is not normal as long as scores are symmetrically distributed, sample sizes equal and, are greater than 12. Variances can differ by a factor of four without type 1 or type 2 error rates rising unacceptably (Keppel and Wickens 2004; Howell 2007). The non-parametric equivalent tests (Kruskal-Wallis) involve an initial process of converting scalar data set to ranks with associated risks of loss of power for this reason the robust parametric ANOVA is advocated in preference (Kinnear and Gray 2009).

Post analytic pairwise comparison used the Bonferonni correction method to determine which group means were significantly different while controlling for the risk of a type II error associated with multiple testing. Partial Eta^2 was calculated to estimate the size of the effect, or change in fatigue and the core set outcome measures following treatment with TNFi therapy.

COMPARING GROUPS AND POST HOC ANALYSIS- CATEGORICAL DATA

Friedman's non-parametric test was used to test the differences between the rank ordered fatigue levels across the 3-time points. Post-hoc analysis was conducted with the Wilcoxon Signed-Rank tests for pairwise comparisons and Bonferroni correction was applied for multiple comparisons, therefore the initial significance level (0.05) was divided by the number of tests conducted (0.05/3 = 0.0166) (Laerd Statistics 2011).

RELATIONSHIP BETWEEN TWO VARIABLES –CONTINUOUS AND ORDINAL DATA

Bivariate descriptive statistics used included contingency tables and correlation procedures. A contingency table was used to describe the frequency distributions between the verbal rating scale and the multidimensional fatigue scale. Correlation statistics were used to describe the association between fatigue and patient demographics, and each of the core set outcome variables. Pearson's' correlation was appropriate for the data on the continuous or scale variable, while Spearman's rank correlation was appropriate for the ordinal data. The Spearman's rank correlation for ordinal data was used to estimate the association between fatigue and patient demographics. The association between the multidimensional fatigue scale and the core outcome measures was estimated using Pearson's correlation coefficient (Kinnear and Gray 2009) for continuous/scale data. Kendall's tau_b (τ_b) was used to estimate the association between the ordinal and continuous data from the two fatigue scales (Kinnear and Gray 2009). Kendall's τ_b represents a probability, specifically, it is the difference between the probability that the observed data are in the same order for the two variables versus the probability that the observed data are in different orders for the two variables, for example, an increase in ordinal scale fatigue (coefficient =.05) is 5% more likely to be associated with an increase, than a decrease, in the multidimensional scale and core set outcome measures (Wolfe 2004; StatSoft 2011).

RELATIONSHIP BETWEEN SEVERAL VARIABLES -FACTOR ANALYSIS

The multivariate technique Factor Analysis, using variamax rotation, was used to disentangle interrelationships between the variables in order to identify clusters of variables related conceptually. Diagnostic inspection of the R-matrix showed, with the exception of

CRP, an association between all variables, which were equal or greater than the minimum recommended correlation of 0.3 for full factor analysis (Appendix 15). Firstly, factor analysis determined the multidimensionality of the multidimensional assessment of fatigue scale and secondly, the existence of any structure in the inter-relationship between fatigue and the core set variables.

RELATIONSHIP BETWEEN SEVERAL VARIABLES –MULTIPLE REGRESSION ANALYSIS

Multiple regression analysis was the other multivariate technique used. Following casewise diagnostics two outliers with absolute standardised residuals > 3 were removed as each were missing fatigue (MAF) data at least one time point. A re-run of the diagnostics confirmed the model assumptions of linearity and homogeneity of variance of the data, and analysis determined the predictive relationship between one dependent variable (fatigue) and two or more independent variables (core set outcome measures).

The independent contribution of fatigue to the overall assessment of outcome in rheumatoid arthritis was calculated and compared with that of the core set outcome measures as follows: data used were the change in the values (Δ) at 3-months, and at (Δ) 6-months, of fatigue and the six core set variables. Each of these seven Δ variables were taken in turn as the independent variable and regressed against the 6 remaining variables to calculate the explained variance ($R^{2)}$), (known as coefficient of determination). This gave a measure of variation in i) fatigue and, ii) in each of the core set variables, that could be explained by the variation in all of the other 6 outcome measures. To provide an estimate of the Unexplained Variance subtraction of R^2 from 1 gave the unexplained variance or independent contribution made by fatigue (Kirwan *et al.* 2007). This was repeated for each of the variables.

RELIABILITY ANALYSIS

Internal consistency of the multidimensional assessment of fatigue scales was estimated using the reliability coefficient Cronbach's Alpha. Normal range is between 0.00 and+1, the higher the reliability the more accurate the measure, values of ≥ 0.70 are an accepted

standard for research tools, and of ≥ 0.90 for clinical tools (Trochim 2006; DeVon *et al.* 2007).

SENSITIVITY ANALYSIS

Sensitivity to change of the multidimensional assessment of fatigue scale and of the core set outcome measures over time was determined and compared through calculation of two separate tests, a paired samples *t*-test and the standardised response mean (SRM) (Walters and Brazier 2003), at both the 3-month and the 6-month time point. The SRM is calculated as the mean change score divided by the standard deviation of the change scores. This measure permitted a comparison to be made between the sensitivity to change of the multidimensional fatigue scale and the sensitivity of the core outcome measures. Results were interpreted according to the following recommendations: SRM's of 0.2 - 0.5 should be regarded as small, 0.5-0.8 as moderate, and > 0.8 as large (Cohen 1988).

The comparative sensitivity to change of each of the fatigue scales for a change in the individual core set outcome measures and the composite DAS28 score was assessed using Kendall's τ_c. This was the appropriate test to use as the two fatigue variables had different categories of data (StatSoft 2011). The data used was the change score from baseline to 3-months, and baseline to 6-months for both fatigue scales.

[Two different variants of *tau* are computed, usually called tau_b and tau_c. These measures differ only with regard as to how tied ranks are handled. In most cases these values will be fairly similar, and when discrepancies occur, it is advised to interpret the lowest value (StatSoft 2011)].

Results were considered statistically significant when p values were < 0.05.

4.8 Comparative, Quantitative, Prospective Study of Persistent Fatigue Confined to the Larger Rheumatoid Arthritis Patient Cohort

4.8.1 Population, sampling, participants

This component of these studies addressed the fourth objective which was to elucidate the unique elements of fatigue. The crux of most debates on predictors and correlates of fatigue centres on whether the dependent variable fatigue is solely attributable to inflammation and disease activity (Crosby 1991), or is a consequence of other independent variables. These other more commonly proposed predictors and contributing factors include disease related factors such as pain, physical conditioning, functional status, and more generic factors like co-morbidities, mood, sleep, psychological and social issues (Tack 1990b; Belza *et al.* 1993). In this second component of the study other predictors of fatigue were explored in a sub-group of patients who were found to demonstrate a moderate to good response to treatment of their active inflammatory disease status. Validated and reliable questionnaires were used to capture information on possible contributory factors such as pain, arthritis self-efficacy, sleep and mood.

The target population was the cohort of patients recruited to the initial longitudinal prospective study (n=130) (Figure 4-3). The sample was selected from the larger rheumatoid arthritis (n=90) cohort for two reasons. Firstly, this diagnostic group was chosen to enhance homogeneity and so the generalisability of findings for this component of study as well as for the supplemental qualitative second phase. Secondly, sampling from this population was more feasible as rheumatoid arthritis is more prevalent than psoriatic arthritis. Inclusion criteria were: -

i) Patients with ‘Poor Fatigue Outcome’, identified 6-months post baseline using agreed disease improvement criteria. These were patients with rheumatoid arthritis who despite demonstrating a moderate to good response in disease activity according to the EULAR Response Criteria (Fransen and van Riel 2005) still continued to report moderate or greater fatigue on the verbal rating scale which ranged from none, through mild, moderate, severe, to very severe.

ii) Patients with 'Good Fatigue Outcome' selected by the researcher to serve as a basis for a control group comparison. These were patients with rheumatoid arthritis who demonstrated a moderate to good response in disease activity according to the EULAR Response Criteria and none or mild fatigue levels on the 5-point verbal rating fatigue scale. Selection criteria reflected the age, sex, functional status according to the HAQ disability index, and disease duration of the *Poor Fatigue Outcome* study group in order to enhance homogeneity of the sample.

Purposive sampling was the strategy used to select the two separate patient subgroups: a *Poor Fatigue Outcome* study group and a *Good Fatigue Outcome* control group. These subsets emerged from the first longitudinal phase of study following statistical analysis. The total sample size was determined by the number of patients who qualified for inclusion in the '*Poor Fatigue Outcome'* study group (n=28; male=6, female=22). The target population, that is, the total number of patients who satisfied the inclusion criteria for the *Good Fatigue Outcome'* control group (n=36), were identified (Figure 5-8). Questionnaires were forwarded to all following initial telephone contact and approval. The first 6 male respondents and the first 22 female respondents who returned completed questionnaires were selected for inclusion in the '*Good Fatigue Outcome'* control group (n=28; male=6, female=22).

4.8.2 Data collection methods and plan

Data Collection Methods

Quantitative assessment of both the *'Poor Fatigue Outcome'* study group and '*Good Fatigue Outcome'* control group was undertaken to elucidate the elements of persistent post-treatment fatigue that were unexplained by the core set of variables. It is acknowledged that medical illnesses like arthritis can contribute to sleep disturbance, and that pain, inflammation, and any variety of psychosocial factors can induce symptoms of excessive daytime sleepiness and fatigue (Wells *et al.* 2009). Validated and reliable questionnaires were used to capture information on possible contributory factors to fatigue such as, a) pain, b) arthritis self-efficacy, c) sleep, and d) mood (Tack 1990a; Wolfe *et al.*

1996; Neuberger *et al.* 1997; Neuberger *et al.* 2007). Scale choice was influenced by evidence of their psychometric properties and validity in rheumatic disease patients. Advice from the resident professor of psychiatry and psychological health, and the documented responder burden was also respected.

a) McGill Pain Questionnaire –Short Form

Pain was assessed in more detail using the multidimensional Short-Form McGill Pain Questionnaire) (Appendix 17) (Melzack 1987; Burckhardt and Jones 2003). This scale was chosen because it provided both quantitative and qualitative assessment of pain in a one page self-administered questionnaire (Melzack 1987). Designed as a generic scale, it contains pain descriptors selected at the time of development based on frequency of their endorsement by patients with a variety of acute, intermittent and chronic pains (Melzack and Katz 2001).

In total this scale provides 5 pain scores: i) sensory, ii) affective, combined into iii) total descriptor score for past week from these pain descriptors; and iv), overall past week pain intensity and v) current pain intensity. The main *Section A* consists of 15 descriptors, rated on a 4 point pain intensity scale: 0=none, 1=mild, 2= moderate, 3=severe. Descriptors 1-11 represent the *sensory* dimension of the pain experience, and 12-15 represent the *affective* dimension. Pain intensity over the past week is captured visually in *Section B* using a 100 mm visual analogue scale, and current pain intensity is captured verbally in *Section C* using 5 descriptive terms (0= 'No pain' to 5= 'Excruciating' pain). The sum of all 15 descriptors make a total score ranging 0–45; this includes the eleven sensory descriptors sum score, ranging 0–33, and four affective descriptors sum score, ranging 0–12.

The Short-Form McGill Pain Questionnaire was designed for minimal user burden in clinical and research settings, it is one page in length, and is easy to administer and score (Melzack and Katz 2006). It takes 2-3 minutes to complete (Burckhardt and Jones 2003). Permission to use the Short-Form McGill Pain Questionnaire was obtained from the author (Appendix 18).

Previously documented psychometric properties include test-retest reliability (intra-class correlation coefficient for total, 0.93; sensory, 0.95; and affective, 0.79 scores), sensitivity to change (>0.80), and modest responsiveness to change (0.61) in a Norwegian population with rheumatic disease pain (Strand *et al.* 2008). Internal consistency reliability was previously demonstrated (Cronbach's α 0.73 to 0.89) in repeated testing of rheumatoid arthritis and fibromyalgia patients (Burckhardt and Bjelle 1994); and in a variety of other different clinical settings (Cronbach's α 0.74–0.87) (Ljunggren *et al.* 2007). The Short-Form McGill Pain Questionnaire has been shown to be a highly reliable measure of rheumatic disease pain, namely osteoarthritis. For the total, sensory, affective, and average pain scores, high intra-class correlations were demonstrated (0.96, 0.95, 0.88, and 0.89, respectively); while the 'current pain intensity' score demonstrated a lower intra-class correlation of 0.75. The coefficients of repeatability, as an estimation of the minimum metrically detectable change, for the total, sensory, affective, average, and current pain components were 5.2, 4.5, 2.8, 1.4 cm, and 1.4, respectively (Grafton *et al.* 2005).

b) Arthritis Self-Efficacy Scales

Patient self-efficacy was measured using The Arthritis Self-Efficacy Scales (ASES) (Appendix 19) (Brady 2003). This scale was chosen as it was originally designed to measure patient's perceived self-efficacy to cope with chronic arthritis. The concept behind this scale is based upon Bandura's self-efficacy theory from the field of behavioural psychology (Bandura 1977). This describes self-efficacy as a behaviour specific belief of an individual's ability to perform a particular behaviour or task (Brady 2003). The ASES was developed by Kate Lorig and colleagues at Stanford University to measure patients' *beliefs* in their own ability to perform certain arthritis self-management tasks, rather than a *measure of actual performance* of any given task (Lorig *et al.* 1989). The emphasis being on the belief in one's ability to execute a task whether or not one does or can perform the specific task (Hewlett *et al.* 2001). Enhanced self-efficacy for certain behaviours has been shown to improve health outcomes in those areas (Lorig 1996). A correlation between improved self-efficacy towards coping with rheumatoid arthritis and lower fatigue levels has been demonstrated (Taal *et al.* 1996). This concept is a central tenet in rheumatoid arthritis self-management programmes (Hewlett *et al.* 2001); and further empirical evidence may provide a theoretical basis for fatigue interventions.

The ASES comprises items such as: *Pain* 'How certain are you that you can make a *large* reduction in your arthritis pain by using methods other than taking extra medication?' *Function* 'How certain are you that you can walk 30 m on flat ground in 20 seconds? and *Other Symptom* "How certain are you that you can do something to help yourself feel better if you are feeling blue?" The *function* and *other symptoms* subscales have been shown to correlate with the HAQ disability Index and Beck Depression Inventory, respectively (Lorig *et al.* 1989).

The ASES includes 20 items divided into 3 self-efficacy subscales*: pain self efficacy* (5-items), *function self efficacy* (9-items), and *other symptoms self efficacy (*6 items- including fatigue). Each item is scored on a Likert scale of 1 (very uncertain) to 10 (very certain). Patients were asked to indicate how certain they are of performing specific tasks with regard to pain, function and other symptoms. The individual subscales are scored separately by calculating the mean of the subscale items. Users are advised that the scale is not valid if one quarter of data are missing, in this case no score is calculated.

The ASES is a self-report questionnaire reflecting current timing. It has been used in numerous studies and clinical trials of self-management intervention in both general arthritis studies (Lorig *et al.* 2004; Lorig *et al.* 2005; Nour *et al.* 2006; Goeppinger *et al.* 2009) and in rheumatoid arthritis specific studies (Taal *et al.* 1993; Smarr *et al.* 1997; Riemsma *et al.* 2003; Hammond *et al.* 2008). The ASES is available in the literature for use in the public domain (Brady 2003; Stanford Patient Education Research Centre 2010).

Validity and reliability were previously demonstrated on a sample of 90 participants in an arthritis self-management programme (Lorig 1996). Internal reliability (Cronbach coefficient alpha) for the three subscales is 0.76, 0.89, and 0.87, respectively. Test-retest reliability for the three subscales ranged from 0.85 to 0.90 (Lorig *et al.* 1989). In a Norwegian study of patients with rheumatoid arthritis, lower scores on the ASES were observed in patients of lower socio-economic groups and those most seriously ill (Brekke *et al.* 1999). The ASES has been recommended as a reliable and valid measure for use in a community-based sample following examination of its comprehensibility, reliability, and validity among British people with arthritis (Barlow *et al.* 1997).

c) Sleep Assessment

Sleep disturbances are recognised as a relatively frequent complication of rheumatoid arthritis (Wegener 1988; Wells *et al.* 2009). Sleep quality and fatigue have been identified by patients with rheumatoid arthritis as important aspects to their overall health and wellbeing (Wells *et al.* 2003a). The Pittsburgh Sleep Quality Index (PSQI) (Appendix 20) (Buysse *et al.* 1989), was used in this study to measure quantitative aspects of sleep such as sleep duration, sleep latency or number of arousals, as well as the subjective aspects of 'depth' or restfulness of sleep during the previous month. The PSQI was chosen for this study as it was previously recommended as a suitable outcome instrument for use in patients with rheumatic diseases (Smith and Wegener 2003). More recently, following a systematic review of sleep instruments, it survived short listing from a list of 45 instruments to a list of 15 instruments, applicable for use in chronic disease, including patients with rheumatoid arthritis (Wells *et al.* 2009).

PSQI comprises 19 self-rated questions and 5 rated by the bed partner or roommate; these latter questions provide information of clinical relevance and are not intended for inclusion in the scoring of the scale. The 19 items are grouped into 7 components, namely, subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medications and daytime dysfunction. Each are equally weighted on a four point 0-3 scale; 0=not during the month; 1=less than once a week; 2=once or twice a week; 3=three or more times a week. The sum of the 7-components yields a global PSQI score ranging from 0-21; higher scores are indicative of worse sleep. The time interval assessed is the past month which is regarded as clinically and scientifically useful (Buysse *et al.* 1989).

The PSQI was designed for ease of use by subjects and ease of interpretation by clinicians and researchers. The estimated completion time is 5-10 minutes and 5 minutes to score. The PSQI is freely available in the public domain along with a free scoring programme using Microsoft Access (Buysse *et al.* 1989; University of Pittsburgh 2010) (Appendix 21).

The PSQI strengths include the applicability of its domains, response characteristics, and psychometric properties. It includes the four domains recently prioritised by patients with rheumatoid arthritis: - 1) sleep adequacy, 2) sleep maintenance, 3) sleep initiation, 4)

daytime functioning (Wells *et al.* 2009). Various studies from clinical psychiatry, primary insomnia patients, and patients with rheumatoid arthritis have shown a global PSQI scores of >5 to be sensitive to (89-99%), and specific for (84-86%), measures of poor quality sleep relative to clinical and laboratory measures (Buysse *et al.* 1989; Backhaus *et al.* 2002; Luyster 2009). An average test retest reliability for global PSQI score was r = 0.87 ($p<0.001$), in a group of 80 patients with primary insomnia (Backhaus *et al.* 2002). The seven component scores of the PSQI demonstrated a high degree of internal consistency (Cronbach's alpha coefficient 0.83), across numerous patient populations with a variety of different physical ailments. Additionally, the PSQI more highly correlated with sleep problems (r = 0.69 - 0.77) than with unrelated constructs, such as mood symptoms and depression (r = 0.22 - 0.65) (Carpenter and Andrykowski 1998). Additionally, global PSQI scores above five (PSQI>5) resulted in a sensitivity of 98.7%, and specificity of 84.4%, to persons with sleep disturbances versus controls (Backhaus et al., 2002).

d) Mood and Depression Scales

This section of study served to add to the body of knowledge on the predictive or explanatory role played by anxiety and depression in the experience of fatigue in rheumatoid arthritis. Three separate scales were used in the assessment of mood: 1) the Profile of Mood States (Appendix 22) (McNair *et al.* 1971), regarded as an objective scale (Shacham 1983), and two subjective scales, 2) the Beck Depression Inventory (Appendix 23) and, 3) the Beck Hopelessness Scale (Appendix 24) (Smarr 2003).

i) The Profile of Mood States (POMS) (McNair *et al.* 1971) is a widely used tool to assess transient, distinct mood states. It has been extensively used in a broad variety of medical patient groups both as a clinical and research instrument (Nyenhuis *et al.* 1999), including patients with arthritis (Ward 1994). The POMS-Short form, promoted for use with patients for whom ordinary tasks might be difficult and time-consuming, was the version used in this study. Available normative data and validation are based on a psychiatric study of outpatient adults and 856 college students, (McNair *et al.* 1971), and a normal adult population (Nyenhuis *et al.* 1999).

The six identified mood factors measured were derived from repeated factor analytic studies and include the bipolar scales; Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, Confusion-Bewilderment. A total of 37 items (adjective check list) are contained within these respective scales. These are measured on a 5-point scale with the options 'not at all' (0), 'a little' (1), 'moderately' (2), 'quite a bit' (3) and 'extremely' (4). One pole, ('Not at all' = 0), represents the positive aspect of 5 dimensions while the other (Extremely=4) measures the negative aspect; the reverse is the case for the sixth dimension vigor/activity. The POMS total mood disturbance score was calculated by summing the scores across the five negative mood categories and subtracting the sum of the 'vigor/activity' category. Low scores indicate a positive mood state (Nezu 2000).

One major advantage of the POMS Short-form is its ease of administration. Estimated completion time is 3-7 minutes in normal health population (Shacham 1983). The researcher's department has collaborative clinical and research links with the local Department of Psychiatry and Mental Health Research from which the POMS manual was available, (permission to use is inherent in departmental purchase).

The convergent and discriminant validity of the POMS has been shown through its correlations with other mood measures. It correlates highly with visual analogue mood scales (VAMS) (Pearson coefficient 0.54-0.70); the POMS total mood disturbance scale correlates with a composite VAMS (r=0.79); the tension-anxiety scale correlates with the State (r=0.72), and Trait score (r=0.70) of the State-Trait Anxiety Inventory (Spielberger and Gorsuch 1983); and with the Beck Depression Inventory (r=0.69). In relation to its discriminant validity the POMS scales have been shown to be consistently more highly related to corresponding mood measures, (for example sad and depressed) (mean r=66.6), than non corresponding mood scales (for example vigor versus inertia) (mean r= 49.5), when compared with other scales (Nyenhuis *et al.* 1999). The POMS has been used in a variety of studies, including rheumatoid arthritis fatigue studies (McFarlane and Brooks 1988; Tack 1990b; Belza 1994; Belza 1995; Dickens *et al.* 2002).

ii) The Beck Depression Inventory **II** (BDI-II) comprises of a series of questions developed to measure the intensity, severity, and depth of depression in adults and

adolescents 13 years of age and older (Beck *et al.* 1961). Its use is to identify the presence and severity of symptoms consistent with the criteria of the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV; 1994) (American Psychiatric Association 1994), rather than serving as an instrument of diagnosis. Its appropriateness as a screening tool for depression in patients with rheumatoid arthritis has been demonstrated (Krug *et al.* 1997).

This study used the long form, composed of 21 questions; each designed to assess a specific symptom common among people with depression. Items 1 to 13 assess symptoms that are psychological in nature, such as mood, pessimism, sense of failure, self-dissatisfaction, guilt, punishment, self-dislike, self-accusation, suicidal ideas, crying, irritability, social withdrawal, while items 14 to 21 assess more physical symptoms, such as body image, work difficulties, insomnia, fatigue, appetite, weight loss, bodily preoccupation, and loss of libido. There is a four-point scale for each item ranging from 0 to 3 (total score range 0-63). A total score of 0-13 is considered minimal range, 14-19 is mild, 20-28 is moderate, and 29-63 is severe (Nezu 2000). The researcher highlighted cases with scores greater than 13 to the treating physicians for appropriate management. These score guidelines are given with the recommendation that thresholds be adjusted based on the characteristics of the sample, and the purpose for use of the BDI-II. This allows for use of clinical discretion when screening for depression (Appendix 25).

The time frame of the questions relates to the previous two weeks. While designed for use by trained health professionals it is also often self-administered; estimated completion time is 5-10 minutes. The researcher's department has collaborative clinical and research links with the local Department of Psychiatry and Mental Health Research from which the BDI=II manual was available (permission to use is inherent in departmental purchase).

The BDI II has been extensively tested for content validity, concurrent validity, and construct validity. Its demonstrated test-retest reliability, one week apart, is 0.93 ($p<0.001$). It has been shown to be highly reliable regardless of the population with results corresponding to clinician ratings of depression in more than 90% of all cases (Beck *et al.* 1988). It has a high construct validity (Cronbach's α= (0.80) and discriminates between depressed and non depressed groups. Factorial validity has been established by the

intercorrelations of the 21 items. The BDI-II can be interpreted as one syndrome (depression) composed of three factors: negative attitudes toward self, performance impairment, and somatic (bodily) disturbance (Beck *et al.* 1988).

iii) The Beck Hopelessness Scale is a 20-item scale for measuring negative attitudes about the future. Although originally developed as a predictor of eventual suicide, the BHS is recommended for measuring the extent of negative attitudes in clinical and research settings (Nezu 2000).

A scoring template is provided to highlight the items marked in the direction keyed for 'hopelessness'; these are summed to provide a straightforward total scale score. Interpretation of results is a recommended combination of cut off guidelines and clinical judgment (Nezu 2000) (Appendix 25). The researcher's department has collaborative clinical and research links with the local Department of Psychiatry and Mental Health Research from which the Beck Hopelessness Scale manual was available, (permission to use is inherent in departmental purchase).

It has an estimated completion time of 5-10 minutes, respondents are asked to tick either true or false in response to 20 short individual statements. For example, '*I look forward to the future with hope and enthusiasm'; 'my future seems dark to me'; I have great faith in the future'.* The psychometric properties of reliability and validity have been extensively demonstrated among patients with mixed diagnoses before and after cognitive therapy intervention, and in hospital and community samples (Dowd 1992; Owen 1992). The scale's internal consistency (measured using KR-20 coefficients) range from 0.82 to 0.93; test retest correlation coefficients between scores were statistically significant at 0.69. The relationship between clinical ratings of hopelessness and BHS scores in two samples: a) 23 outpatients in a general medical practice, and b) 62 hospitalised patients who had recently attempted suicide demonstrated its concurrent validity. In the general practice sample, the correlation between the BHS and the ratings of hopelessness was 0.74; in the suicide-attempt sample, it was 0.62.

Data Collection Plan

This phase of study was undertaken as a postal questionnaire survey in order to quantify elements of fatigue that cannot be explained directly by disease status in rheumatoid arthritis. All instruments chosen for this section of the study had previous evidence of high reliability and validity and of their use in international research. The feasibility element of all questionnaires combined was favourable with regard to ease of application of the instruments, and in relation to respondent burden or time demand, cost of production and interpretability (Boers *et al.* 1998; Minnock *et al.* 2009). As a test, the researcher completed the questionnaires within 20 minutes and advised all participants during telephone contact that completion would take between 20-40 minutes of their time. The questionnaires were compiled into a booklet format labelled with the patients' study identification number for identification purposes. Colour coding was used to distinguish study and control group respondents in order to facilitate data management.

4.8.3 Study procedure and permission process

Telephone contact was made with each individual patient in advance of forwarding them the questionnaire booklet and their permission to participate in this section of the study was re-confirmed verbally. The researcher diligently ensured that no patient was forwarded the survey material prior to telephone contact having been established. No patient declined participation. This action probably served to ensure the 100% response rate received from both subgroups. All patients were forwarded a postal package which contained a cover letter containing contact details for the researcher, a patient consent form (Appendix 14), the questionnaires compiled in a booklet format, and a prepaid, addressed envelope for return of questionnaires. The majority of responses were received by return post within one month of issuing the survey. One follow up reminder telephone call was made to 14 patients, with success, 3 weeks following postal, and an arrangement to meet one patient when she attended a clinic appointment 3 months following postal, ensured a 100% return of completed questionnaires. This proved to be a positive data collection experience.

4.8.4 Analytical procedure and methods

The computer software package Microsoft Excel and the statistical package SPSS 16.0 for Windows (SPSS.com 2009) were used to analyse the data. Descriptive and inferential statistics were employed. Key variables (McGill Pain Questionnaire, Arthritis Self-Efficacy Scale, Pittsburgh Sleep Quality Index, Profile of Mood States, Beck Depression Inventory, Beck Hopelessness Scale) were tested for normality of distribution of the data using the Shapiro-Wilk test, a significance value greater the 0.05 representing data normality (Kinnear and Gray 2009). All variables deviated from a normal distribution with the exception of Self-Efficacy Pain Scale (Appendix 15).

Univariate descriptive statistics were used to report patient demographics, disease characteristics; pain, arthritis self-efficacy, sleep, and mood variables. Numbers and percentage counts were reported for nominal data (education/smoking status/rheumatoid factor), mean and standard deviations were reported on the normally distributed variables such as the (DAS28), and medians and range for skewed data such as Haemoglobin, and early morning stiffness. Data were presented numerically.

Inferential statistics to test for differences between subgroup means included chi-square test of association for nominal data (rheumatoid factor), the parametric independent sample t-test for group means on the normally distributed scale variables, (HAQ-disability index and Haemoglobin, self-efficacy for pain), and the non-parametric Mann-Whitney U test in data which deviated from the normal. Results were considered statistically significant when *P* values were < 0.05. As the sample size was small the exact *P* value in preference to the asymptotic *P* value along with the *Z* approximation test were reported.

4.9 Qualitative Descriptive Study of a Volunteer Group of Patients with Rheumatoid Arthritis and Poor Fatigue Outcome

The second phase of study undertaken was a supplemental component using a qualitative approach to inquiry. The empirical method of investigation used was qualitative description.

Semi-structured individual interviews with open ended questions were used to further elucidate the unique elements of fatigue and to further explore patients' perceptions, evaluation, and outcome in relation to persistent fatigue. The narrative data were subjected to the technique of qualitative content analysis (Graneheim and Lundman 2004). The aim was to describe patients' perceptions and experiences of the phenomenon of fatigue in order to address the fourth and fifth objectives of study, namely, to elucidate the unique elements of fatigue and, to identify from patients' experiences potential modifiable factors to improve fatigue outcome.

4.9.1 Population, sampling, participants

The population consisted of patients with rheumatoid arthritis who demonstrated a moderate to good response in disease activity according to the EULAR Response Criteria who continued to report moderate or greater fatigue on the five point verbal rating scale which ranged from none, through mild, moderate, severe, to very severe. Patients identified, with '*Poor Fatigue Outcome*', following analysis of the dominant quantitative phase of study, were eligible for interview (Figure 4-3). Purposeful sampling technique used criterion sampling in the first instance, followed by a consecutive approach to patient recruitment (Polit and Beck 2010a). That is, consecutive patients from the population who met the eligibility criterion, and scheduled to attend for a clinic appointment over the 3-month data collection period within the study timeframe, were identified.

4.10 Study Procedure and Permission Procedure

The researcher made telephone contact with the identified eligible patients to invite them to participate. For patient convenience a time for interview was arranged to coincide with the day of their forthcoming clinic appointment. Prior to interview the researcher reiterated the intention to record the interview and obtained written consent from each patient (Appendix 14). The participant information portion of the consent form was retained by the patient; the signed and witnessed consent form was filed by the researcher in the study register. This process of patient recruitment continued during the period of data collection.

4.10.1 Data collection method and plan

A semi-structured style of interviewing with open-ended questions was used to collect narrative data through 10 face to face interviews with patients (Neergaard *et al.* 2009). This is advocated when the researcher knows what they wish to ask but are unable to predict the answers (Morse and Field 1996). The interview focused on areas that were both poorly understood, such as fatigue experience, and also potentially amenable to intervention, that is factors that might improve fatigue outcome. The prepared interview guide (Appendix 25) ensured that no domain of interest was forgotten while at the same time providing scope for the patients to freely respond giving a broad insight into the subject of fatigue. To seek the overall perspective of the participants and avoid "premature closure", the initial questions were open and broad, and sought information on the meaning, experience of fatigue and self-care methods of management. This included 'why', 'how' and 'what' questions related to patients view, motives and behaviours in relation to their fatigue experience, as detailed in Appendix 25. A sample of 10 interviews was considered adequate when there was no emergence of new data, reflecting data saturation (Patton 2004; Milne and Oberle 2005).

All the interviews were conducted in a dedicated private interview room, adjacent to the clinical area, only the patient and researcher were present. All interviews were digitally recorded. The audio equipment was tested in the presence of, and with the cooperation of the patients each time. These actions helped to serve as an 'ice breaker' and facilitated the development of a relaxed atmosphere and rapport for the formal interviews. Each interview

lasted from 35 minutes to 60 minutes; the majority were of 45 minutes duration. The interviews were listened to and re-listened to and subsequently transcribed in full, using the services of a professional transcribing agency. A reflective journal was kept by the researcher to record in-field memos, and the context of data- gathering episodes, and to help counter bias (Thorne *et al.* 1997). As requested by 2 patients copies of their transcribed scripts were forwarded to them. No repeat interviews were carried out. Data coding was conducted by the researcher, and the project supervisor reviewed the transcripts.

4.10.2 Analytical procedure and methods

Data were analysed using the technique of inductive content analysis. The flexibility of this content sensitive method is compatible with a mixed methods design; while the inductive reasoning approach permitted movement from specific observations to broader generalisations (Cavanagh 1997; Sandelowski 2000b; Neergaard *et al.* 2009). As a method content analysis is concerned with meanings, intentions, consequences and context (Elo and Kyngäs 2008), as well as an enhanced understanding of phenomena (Cavanagh 1997). The steps taken followed those generally encompassed in the analytical process: - selection of unit of analysis, creating and defining categories, revision and reiteration of the process to ensure trustworthiness, abstraction and reporting of findings. These steps were conducted in a non-linear manner as the researcher engaged in a back and forth movement between the data and the findings.

These steps were applied in this study as follows. Interviews were read through several times by the researcher to obtain a sense of the overall content in its entirety (Downe-Wamboldt 1992; Graneheim and Lundman 2004). The narrative data from the interviews formed the ‘unit of analysis’. Data reduction was done manually through a system of highlighting and coding. ‘Meaning units’ were identified from the unit of analysis which comprised of a constellation of words, sentences, or paragraphs related to the same central meaning. These were further reduced into ‘condensed meaning units’ (Graneheim and Lundman 2004). The language used to record the condensed meaning units was taken directly from the interview text ensuring that a rich, straight description was obtained by

staying close to the data (Neergaard *et al.* 2009). These condensed meaning units were abstracted and labelled with a code. The whole context of the interview was considered when condensing and labelling meaning units with codes (Graneheim and Lundman 2004). The codes were compared and contrasted for similarities and dissimilarities and further reduced to categories. The final steps taken by the researcher was the identification of 'an overarching theme,' through reflection and low grade inference, in order to express the 'latent content' of the data.

Initially, comments and emergent categories were documented in margins either side of the text. The process was then documented electronically and displayed in a flow chart created in a Microsoft Word document from which patient responses were examined and compared within and across categories. The end results were displayed in a table with clusters of categories/sub-categories from which main categories and an overarching theme was identified. This process of content analysis allowed the distillation of words into fewer content related categories based on the underlying premise that when words and phrases are classified into the same categories they share the same meaning (Elo and Kyngäs 2008). The categories and theme identified were reported textually and graphically through the use of a conceptual model (Figure 5-9).

4.10.3 Rigour

Strategies and their associated techniques to enhance trustworthiness in qualitative description were employed throughout this qualitative supplemental phase to ensure credibility, and transferability (Graneheim and Lundman 2004). Credibility of this supplemental component of study was addressed by ensuring that selection criteria and patient recruitment were both appropriate to the study objectives. To facilitate transferability detailed descriptions of the context, selection, and characteristics of the study participants and of the data collection process are provided in this chapter with further elaboration in the results section (Graneheim and Lundman 2004).

Patient participants were confined to those with persistent fatigue despite an improvement in disease activity status in order to gain insight on the patients' perspectives of

unexplained elements of fatigue, and potential options for interventions. Similarly, patients interviewed were of various ages, disease duration, gender, and different disease and life experiences. Open ended questioning ensured the primacy of patients' opinions and perspectives (Milne and Oberle 2005). The method of recruitment and data collection procedures were tested in practice interviews conducted during the month prior to the study data collection period. Two patients were interviewed to test the feasibility of the methods, and to provide training in interview technique. These data were subsequently excluded from the analysis as these interviews served as training for the researcher whose previous experience in conducting qualitative interviews was at undergraduate level.

This qualitative study was part of a PhD studentship conducted by a female researcher with many years of clinical rheumatology nursing experience. This clinical experience contributed to a relaxed style of interviewing which enhanced the flow of rich contextual data. Throughout the study the researcher continued to work as a nurse practitioner. Only two of the patients interviewed were previously known to the researcher in a professional capacity. The researcher's first time ever to meet the other patients was at the scheduled interview time. The researchers' background interest in fatigue and health outcomes research in patients with a rheumatic disease, both locally and internationally, was shared with the interviewees.

All interviews were transcribed verbatim by an external agency. To ensure authenticity of the data the researcher both listened to the recordings, read the transcripts repeatedly and frequently returned to the transcripts to ensure that the analysis remained true to the expressed sentiments of the patients. This iterative process was used to assess and enhance the trustworthiness of the analytic process (Downe-Wamboldt 1992; Graneheim and Lundman 2004). Analysis of data content placed emphasis on what was said, and used a low inference approach, on the suggested meaning of the spoken word (Neergaard *et al.* 2009). The process of data reduction, display, analysis and abstraction is described in detail in the results section (Section 5.17). Findings were further authenticated with representative quotations from the transcribed text used to illustrate the various categories of data including the similarities within each and the differences between categories, and to substantiate claims made about data (Sandelowski 2000b; Patton 2004). In order to

contribute to understanding of and trustworthiness in this process of content analysis these categories are succinctly presented to the reader in a conceptual model (Figure 5-9).

Other methods used to enhance the rigour of the qualitative data included the sufficient collection of data to fulfill the research objective, and provide a comprehensive insight into the fatigue experience. Further steps taken included “negative” or “deviant” case analysis to highlight any interview comments in disagreement with the prevailing trend, and peer debriefing by a neutral PhD research colleague who reviewed data transcripts ‘blind’ for comparison with the researcher’s view (Mays and Pope 1995). The presentation of authentic citations serves to demonstrate the source and process of category and theme development from the narrative data (Sandelowski 2000b). Similarities and dissimilarities between the categories were discussed with the project supervisor, trustworthiness was further enhanced by ongoing discussion with, and peer review of the process and outcomes, by both the clinical and academic supervisors (Polit and Beck 2010a).

To conclude, Figure 4-3 provides a succinct visual summary of the research methodology representing the phases, procedures, methods of data collection and product, of this sequential mixed methods explanatory design study.

Figure 4-3: Visual model of the sequential mixed methods explanatory design: phases, procedures, methods of data collection employed, and product

Study Phase	Procedure	Product
PHASE 1 1:1 Longitudinal Study 1:2 Comparative Study Components **Quantitative Data Collection**	**Phase 1:1** Longitudinal, quantitative, prospective, descriptive study designed to fulfil objectives I-III (n=130). Clinical assessment and participant completed questionnaires at 3 separate time points; 0, 3 & 6 months. **Phase 1:2:** Comparative, quantitative, prospective study of poor and good fatigue outcome subgroups- designed to address objective IV. Postal questionnaire design survey, (n=28, 28). Deductive analysis.	Clinical derived numeric data, Biochemical derived numeric data Patient reported outcomes numeric data i.e. self-completed questionnaires for both studies.
Quantitative Data Analysis	Data collection, coding and input to SPSS16 quantitative software programme Frequencies, and descriptive statistics, ANOVA, Correlations and Factor Analysis, Multivariate regression analysis Tests of Significance (parametric and non parametric)	Normality, outliers, missing data, Central tendency, dispersion numeric and graphic presentation, Associations, causation, Inferential statistics associations & differences
Connecting Quantitative and Qualitative Phases	During formulation of purpose and objectives, Phase 1 data analysis determined Phase 2 participant selection,	Narrative data Semi-structured interview protocol,
PHASE 2 qualitative Data Collection	**Phase 2:** A qualitative study of a volunteer group (n= 10) identified through the preceding quantitative phases, designed to address objectives IV-V, Individual in-depth semi-structured interviews (n=10).	10 Audio interview recordings and 10 Transcriptions of narrative data
qualitative Data Analysis	Inductive Content Analysis Data reduction, display and abstraction of meaning Unit of analysis Meaning units Condensed meaning units Codes, Categories, Themes	Similar and different, categories, Visual model of analysis, representing one overarching theme, 4 main categories, incorporating subcategories
Integration of Quantitative and qualitative Findings	Interpretation and explanation of the QUANTITATIVE and qualitative results and integration of findings	Discussion, Implications Limitations Future research

4.10.4 Ethical considerations

Background

Scientific research involving human subjects must satisfy internationally agreed and recognised codes of ethics. These were largely developed over the latter half of the 20th century to prevent human rights violations. The most significant are i) The Nuremberg Code (1948): post World War II atrocities and regarded as the original prototype, ii) The Declaration of Helsinki (1964): established by the World Medical Association, subsequent revisions form the basis of Good Clinical Practices used today, and iii) The Belmont Report (1979): The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was established in 1974 by the National Research Act (Pub. L. 93-348), enacted by the United States Congress. The Commission drafted the Belmont Report (1979) which states the basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects (Office for the Protection of Research Subjects ; Polit and Beck 2010a).

The design and conduct of this study on fatigue in patients with inflammatory arthritis was subject to these three basic principles relevant to the ethics of research involving human subjects and their corresponding applications. These three principles are: -

1. Respect for persons: Individuals should be treated as autonomous agents; Persons with diminished autonomy are entitled to protection.	Study application: Subjects, to the degree that they were capable, were given the opportunity to choose what shall or shall not happen to them in relation to study participation, The consent process included three elements: information, comprehension, and voluntariness.
2. Beneficence: Human subjects should not be harmed; Research should maximize possible benefits and minimize possible harms.	Study application: The nature and scope of risks and benefits were assessed in a systematic manner and openly discussed with study participants. Potential for harm was minimal in this study.
3. Justice: The benefits and risks of research must be distributed fairly.	Study application: Fair procedures and outcomes in the selection of research subjects were ensured throughout the study process from design to dissemination of findings.

4.10.5 Details of ethical approval

Prior to commencement of data collection and in keeping with local requirements this study was approved by the Ethics and Medical Research Committee, of the study site (Appendix 27). As this was a doctoral study ethical approval was also required and granted by the Faculty of Health Sciences Ethics Committee, Trinity College Dublin (Appendix 28).

The overarching aim of this scientific study was to contribute to the standardisation of assessment of fatigue and rational development of appropriate therapeutic interventions to treat and promote management of disabling fatigue. Achievement of this aim has the potential to produce a substantial social benefit to patients with inflammatory arthritis (Office of Human Subjects Research).

Respect for potential study participants was safeguarded through a combination of the rigorous recruitment procedures and provision for informed consent. Information was given verbally to patients by the gatekeepers, and in written form through the ethically approved Participant Information Leaflet and Consent Form *(*Appendix 13 and Appendix 14). The study gatekeepers facilitated patient's right to decline participation in the first phase of study, if they so wished, as they were not directly invited to participate by the researcher, which might have made it more difficult for patients to decline. Patients were also given the opportunity to reiterate, or otherwise, their consent to complete the second component of study, the postal survey, when telephone contact was made by the researcher in advance of posting questionnaires, and also by voluntary nature of completing and returning these. Patients were given a two week interval from being informed about the study at time of recruitment to consenting in writing to participate. None of the patients recruited were from potentially vulnerable groups (adults with learning disabilities, communication difficulties or mental illness) where extra steps to safeguard their comprehension, voluntariness, confidentiality would have been required, as specified in the ethical application.

To safeguard confidentiality, all data extracted from clinical data files and collected exclusively for the study (hard copies), were processed and stored in a locked filing cabinet or password protected computer (electronic data), in accordance with the Data Protection

(Amendment) Act (2003). Participants were assigned a study ID number. The master list of names with identifiable ID numbers was stored securely away from all other data. Data collection booklets containing all the quantitative measurement instruments, for all participants (containing evidence for study eligibility, consent, clinical findings, outcomes, required laboratory data), and interview transcripts will be retained by the principal researcher in a secure storage facility for at least five years after the completion of the research, as required by University of Dublin, Trinity College Dublin regulations. Further steps were taken to safeguard the privacy of participants in the qualitative strand. All interview transcription was rendered anonymous prior to submission for typing. The researcher used known transcribers who agreed to strict adherence to codes of conduct in order to preserve the participants' anonymity, privacy and confidentiality. All electronic records are backed up in password protected files.

The application of the principal of beneficence dictated that this study should maximize potential benefits and minimize possible harm. This was a non-invasive study. Involvement in this study included routine clinical assessment, questionnaire completion and semi-structured interviews of a sub-group of patients. No risks or adverse outcomes due to participation were expected or realised. Patients were free to withdraw at any time from any phase of the study and to decline any questions that they did not feel comfortable with. The chief investigator was an Advanced Nurse Practitioner (Rheumatology) with 26 years clinical experience in the speciality and 10 years experience as a clinical researcher, primarily in the area of patients perceptions, and is sensitive to the needs of this client group. The study progress and outcomes from international fatigue studies were shared with patients following the qualitative interviews who were especially curious in this regard following their own disclosures. Learning about fatigue was and continues to be shared by the researcher with patients and colleagues in clinical practice in order to contribute to improved management of this symptom.

The use of the Beck Depression Inventory in the second component of the study identified patients with a depressive mood state. These patients were contacted by phone and sensitively informed that the questionnaire they completed highlighted some 'low mood'. A supportive interview session was provided and all patients availed of either a psychosocial

consult and or a rheumatology clinical review, by the researcher and medical consultant, of their current disease status to help with their difficult emotional state at that time.

While patients may not have benefited directly from taking part in this study the information obtained will inform the body of knowledge on fatigue and contribute to the development of strategies for better management of this symptom. This close level of monitoring that was part of the study can sometimes have therapeutic benefits and it is believed that this was the case particularly for those identified to have a low mood state. Clinical problems were also brought to the fore during telephone contact prior to the postal survey and appropriate care was expedited without delay in these cases (change of treatment, advance of next clinical review date, rehabilitation therapy). There is agreement amongst the wider rheumatology community that work should be done to provide the evidence base for the rational development of appropriate therapeutic interventions to treat and promote self-care and professional management of this salient symptom. This study addressed both these issues to enable the development of appropriate methods to address this deficit in patient care.

Benefits and risks of research were balanced fairly through judicious selection of research subjects, fair procedure and outcomes, and the right to privacy (Office of Human Subjects Research ; Polit and Beck 2010a). All patients satisfying the criteria were offered the option of non-participation and the right to withdraw without prejudice to care, assured of confidentiality, and were given the researcher's contact details, and an offer to answer any questions. Patients were informed that the results of the study will be published both nationally and internationally and that their anonymity is guaranteed in all presentations and publications.

Chapter 5 RESULTS

This chapter reports the results of this mixed methods study. Firstly, the results from both components of the initial dominant quantitative phase are presented. Secondly, findings from the non-dominant qualitative phase are presented.

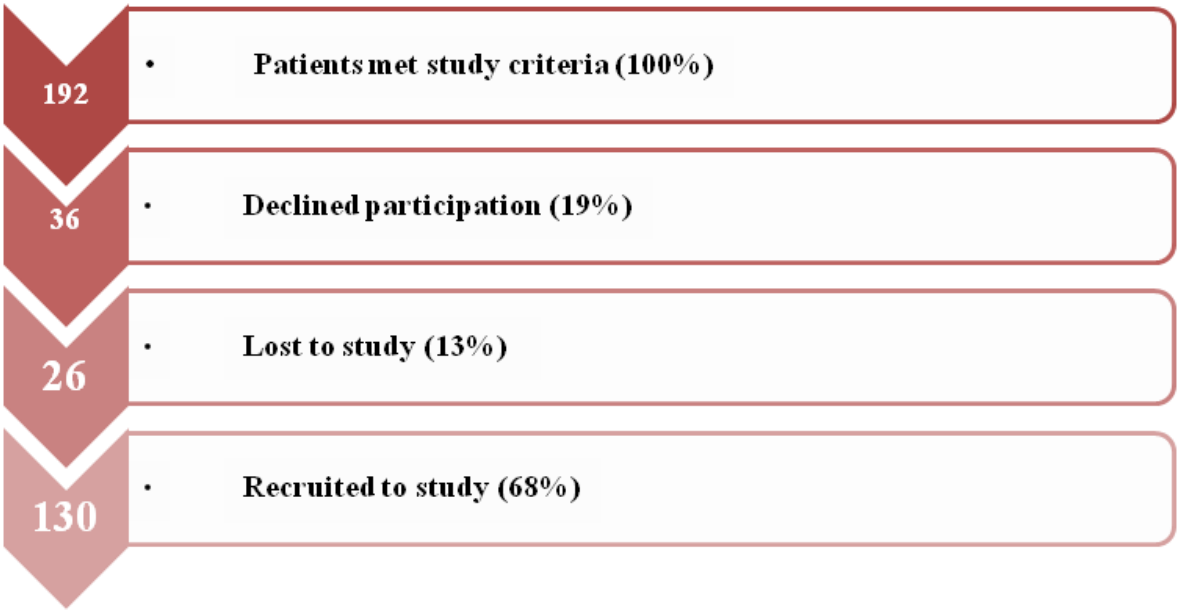
5.1 Patient Characteristics: Demographic and Clinical Details

The demographic details and key clinical characteristics of the study group of patients, with inflammatory arthritis prescribed TNFi therapy, at the three separate times of clinical assessment over a 6-month period, are first presented. Normally distributed data are presented as means ± (SD); range and median values are reported on data that deviate from the normal distribution (Appendix 15).

One hundred and ninety-two patients satisfied the inclusion criteria. Thirty six patients declined recruitment into the fatigue study from the outset. A further 26 patients were lost to the study due to a combination of three main factors: 19 patients elected to continue their follow-up care through alternate private health care practices, 2 patients had their care continued through the general rheumatology clinic as opposed to the specialised biologic clinic services, contraindications to TNFi therapy were detected during the pre-screening stage for 5 patients (3 suspect malignant skin lesions, and 2 required treatment for latent pulmonary tuberculosis).

The further attrition of participants for follow-up appointments at 3-months and 6-months was due to a combination of factors: missed attendance (frequently due to good response to treatment), either treatment interruption or termination for medical reasons, and exclusion due to non-response to all components of patient reported outcomes. Recruitment and data collection for this longitudinal phase of study was complete within the projected 2–year period.

Figure 5-1: Study population, attrition and sample



The final study sample therefore consisted of one hundred and thirty patient baseline assessments (n=130), one hundred and twelve 3-month assessments (n=112), and eighty seven (n=87) 6-month assessments, following commencement of TNFi therapy (Figure 5-1). Key baseline variables, including age, disease duration, Haemaglobin, Early Morning Stiffness, multidimensional assessment of fatigue, and DAS28-CRP score, of these 87 participants did not differ from those of the 43 participants who were lost to follow-up at 6-months (Appendix 16)

A description of the key demographic and clinical details of the study cohort is provided in Table 5-1. Demographic details of the respondents and those who declined participation were largely similar. Eighty-seven respondents (67%) were female, mean age ± SD (range), years was 52 ±13 (23-81) years, mean disease duration, years 11.7 ±11 (1-39). Sixty-two patients (48%) tested positive for rheumatoid factor, ninety (69%) had a diagnosis of rheumatoid arthritis and the remaining forty (31%) were patients with psoriatic arthritis. Patients were prescribed one of three biologic medication: Adalimumab, (55%), Etanercept (39%), or Infliximab (6%).

Table 5-1: Summary of key demographic and clinical characteristic at baseline

Demographic and Clinical Details		n (valid %)
Female gender (n=130)		87 (67)
Mean age ± SD (range), years (n=128)		52±13(23-81)
Mean disease duration ± SD (range), years (n=128)		12±11(1-39)
Rheumatoid Factor (n=130)	Sero-positive	62 (48)
Diagnosis	Rheumatoid arthritis	90 (69)
(n=130)	Psoriatic arthritis	40 (31)
Biologic Drug:	Adalimumab	72 (55)
(n=130)	Etanercept	50 (39)
	Infliximab	8 (6)
Smoking Status:	Current	39 (34)
(n=114)	Previous Smoker	30 (26)
	Non-smoker	45 (40)
Educational Background	Primary	22 (22)
(n=102)	Secondary	40 (39)
	Third	40 (39)
Ever Failed DMARD	Yes	83 (64)
(n=130)	No	47 (36)
Ever Failed Biologic Drug (n=128)	No	3 (2)
Median Haemoglobin Levels (range), g/dl:		
(n=77)	Baseline	13.0 (7-16)
(n=58)	3-months	13.7 (11-17)
(n=72)	6-months	13.4 (9-17)
Mean Early Morning Stiffness range, minutes		
(n=126)	Baseline	40 (0-1440)
(n=108)	3-months	10 (0-1440)
(n=55)	6-months	15 (0-180)

DMARD- disease modifying anti-rheumatic drug

5.2 Clinical Disease Characteristics

The clinical disease characteristics of inflammatory arthritis in the study cohort are presented in (Table 5-2). These were captured using six core set outcome measures at baseline; and 3-months, and 6-months following commencement of TNFi therapy.

Table 5-2: Core set clinical disease characteristics at baseline; and 3 and 6-months following TNFi therapy

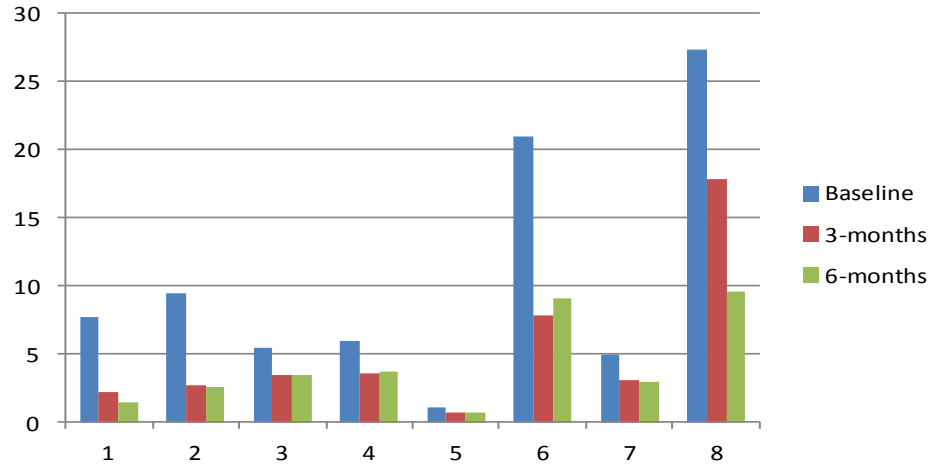
Clinical Disease Characteristics#		Median (range)	Mean±SD	ANOVA p-value
Swollen Joint Count-28 (SJC)	Baseline (n=125)	7.0 (0-28)	7.7 ± 6.2	
	3-months (n=111)	1.0 (1-14)	2.2 ± 3.0	
	6-months (n=85)	1.0 (0-13)	1.5 ± 2.3 **	p<0.001
Tender Joint Count-28 (TJC)	Baseline (n=125)	8.0 (0-28)	9.4 ± 7.8	
	3-months (n=111)	1.0 (1-22)	2.7 ± 4.2	
	6-months (n=85)	1.0 (0-28)	2.6 ± 4.9 *	p<0.001
Pain (0-10)	Baseline (n=125)	5.0 (1-10)	5.5 ± 2.1	
	3-months (n=111)	3.0 (1-8)	3.4 ± 2.3	p<0.001
	6-months (n=87)	3.0 (0-9)	3.5 ± 2.1*	
Global Health (GH) (0-10)	Baseline (n=126)	6.0 (1-10)	5.9 ± 2.2	
	3-months (n=112)	3.0 (1-10)	3.6 ± 2.4	p<0.001
	6-months (n=87)	3.0 (0-9)	3.7 ± 2.1*	
HAQ-disability index (0-3)	Baseline (n=125)	1.125 (0-2.5)	1.070 ± .67	
	3-months (n=105)	0.75 (0-3)	0.749 ± .73	p<0.001
	6-months (n=82)	0.625 (0-2.8)	0.738± .67*	
C-Reactive Protein (CRP) (0-30 mg/l)	Baseline (n=126)	10 (2-155)	21.2 ±27.4	
	3-months (n=108)	4 (0-71)	7.8±12.1	p<0.001
	6-months (n=85)	0.5 (0-105)	9.1 ± 9.1*	
Disease Activity Score-28 (DAS28)[¥] (0-10)	Baseline (n=120)	4.8 (1.7-7.9)	4.9 ± 1.2	
	3-months (n=106)	2.9 (1.4-6.5)	3.1 ± 1.1	p<0.001
	6-months (n=83)	2.7 (1.2-7.1)	2.9 ± 1.1 *	

HAQ, Health assessment questionnaire-disability index. # See Chapter 4:6:3 Core Set Variables. [¥] See Section 4.7 and Table 4-1 DAS28; and Table 4-2 Eular Response Criteria. ANOVA Analysis of variance. * Significant at the 0.05 level. ** Significant at the 0.01 level.

All data deviated from the normal distribution with the exception of DAS28 at baseline (Appendix 15). Non parametric tests were employed in all statistical analyses; for clarity and ease of comparison with the literature both median (range) and mean (SD) values are presented.

The clinical characteristics reflect active inflammatory disease prior to the commencement of treatment with this biologic therapy (TNFi). Change in the level of disease activity captured at both 3-months, and at 6-months follow-up are summarised in Table 5-2. Following initiation of TNFi therapy a consistent fall in the scores of the outcome measures was demonstrated. Changes in the core set outcome measures from baseline captured at 3-months, and at 6-months are represented in Figure 5-2. The fall in levels of all variables reflects an improvement in disease status over time.

Figure 5-2: Change in core set outcome measures over the three time points



SJC: Swollen Joint Count 28. TJC: Tender Joint Count 28. Pain VAS: Pain visual analogue scale. GH: Patient Global Health; HAQ: Health Assessment Questionnaire-disability index: CRP; C-reactive protein: DAS28; Disease Activity Score 28.

The one-way analysis of variance (ANOVA) method was used to determine the significance of these improvements over time in the entire core set outcome measures. The mean differences were significant at the 0.05 level. Post-hoc analysis used the Bonferroni adjusted method for multiple testing in the pairwise comparison of the means of all outcome measures between the time points. Partial Eta^2 was also calculated to measure effect size. Size of effect was evaluated using Cohen's *f*: small $0.10 \leq f. < 0.25$; medium

$0.25 \leq f. < 0.40$; large $f \geq 0.40$, (Kinnear and Gray 2009). Results of ANOVA and post-hoc analyses are summarised in Table 5-3.

All outcome measures improved significantly over time; the greatest improvement in all variables occurred between baseline and 3-months. Only two of the three pair wise comparisons were found to be significant. For the entire core set of outcome measures the changes demonstrated between baseline and 3- months, and between baseline and 6-months were found to be statistically significant. Between the 3-month and 6-month time points no further reduction in swollen and tender joint counts, pain, and patient global health was observed; while further reduction in the value of the HAQ-disability index, CRP, and composite DAS28 was observed this trend failed to reach statistical significance.

Table 5-3: ANOVA, effect size and pairwise comparison between the core set variables at the 3 time points

Core Set Outcome Measures	ANOVA		Pairwise Comparisons Bonferroni adjustment	
	(df)F:p	Partial Eta^2	0-3 months	0-6 Months
Swollen Joint Count-28	*F* (2, 98) = 70.1: p <0.001*	0.50	<0.001	<0.001
Tender Joint Count-28	*F* (2, 119) = 54.4: p <0.001*	0.44	<0.001	<0.001
Pain (0-10)	*F* (2, 136) = 21.8: p <0. 001*	0.24	<0.001	<0.001
Global Health (0-10)	*F* (2, 127) = 31.9: p < 0.001*	0.31	<0.001	<0.001
HAQ(0-3)	*F* (2, 124) = 20.9 p <.0.001*	0.25	<0.001	<0.001
CRP(0-30 mg/l)	*F* (2, 114) = 18.1: p <0. 001*	0.20	<0.001	<0.001
DAS28(0-10)	*F* (2, 134) = 38.7: p <0. 001*	0.67	<0.001	<0.001

HAQ; Health Assessment Questionnaire-disability index: CRP; C-Reactive protein. DAS28; Disease Activity Score 28. MAF, Multidimensional Assessment of Fatigue Scale. * Significant at the 0.05 level.

Large effect sizes were seen for swollen joint count and tender joint count (Partial Eta^2 = 0.50) and (Partial Eta^2= 0.44). The effect size for global health (Partial Eta^2 = 0.31) and for the HAQ disability index (Partial Eta^2 of 0.25) were in keeping with a medium effect size; whereas those for pain (Partial Eta^2 = 0.24) and for C-reactive protein (Partial Eta^2 = 0.20) were small. The composite DAS28 demonstrated the largest effect size (Partial Eta^2 = 0.67).

These changes in disease characteristics as measured by the conventional core set of outcome measures following treatment with TNFi therapy represent an overall improvement in disease status. This improvement was most significant between baseline and 3-month follow-up and was maintained at the 6-month follow-up. The improved disease status is captured in the change in the mean ± (SD) composite Disease Activity Score28 which fell from a high level at baseline (4.9± 1.2), to a low level at 3-months (3.1± 1.1), and 6-months (2.9± 1.1).

5.3 Disease Activity Scores and EULAR Response Criteria

The mean disease activity score and the measure of response following initiation of treatment are summarised (Table 5-4). The DAS28 was available for 119 (92%) patients (rheumatoid arthritis and psoriatic arthritis) at baseline, 106 (82%) patients at 3 months, and 83 (64%) patients at 6 months. EULAR response criteria were available for 99 (76%) patients at 3 months and 79 (61%) patients at 6 months. Based on attained levels of change from baseline (Δ) the proportion of patients classified as moderate responders at 3-months was 43%, and as good responders was 42%; at 6-months the proportion of patients classified as moderate responders was 40%, and as good responders was 60%.

Table 5-4: Disease activity at baseline and improvement scores 3-months and 6-months post initiation of anti TNF therapy

Disease Activity Score (DAS)28*	**Score**	**Baseline** n valid (%)	**3-months** n valid (%)	**6-months** n (valid%)
Remission	<2.6	0	40 (38)	33 (40)
Low disease activity	>2.6 ≤ 3.2	8 (7)	19 (18)	22 (27)
Moderate disease activity	>3.2 ≤ 5.1	52 (44)	41 (39)	25 (30)
High disease activity	>5.1	58 (49)	6 (6)	3 (3)
Available DAS28 scores n (% total)		*119 (92)*	*106 (82)*	*83 (64)*
EULAR Response Criteria (ERC)**	**DAS-28 Δ**	**Δ 0-3 months** n (%)		**Δ 0-6 months** n (%)
No response	≤ 0.6	14 (14)		0
Moderate response	> 0.6 ≤ 1.2	43 (43)		32 (40)
Good Response	> 1.2	42 (42)		47 (60)
Available ERC scores n (% total)		*99 (76)*		*79 (61*

See *Table 4-1: Disease Activity Scale 28; **Table 4-1 and Table 4-2;

Disease activity classified according to the DAS28 demonstrated a consistent improvement between baseline and 3 months, between 3 months and 6 months, and between baseline and 6-months. At 6-months a moderate to good response was demonstrated in all 79 patients for whom calculation of the EULAR response criteria was possible.

5.4 Fatigue Levels in Patients with Inflammatory Arthritis: at Baseline; and 3 and 6 Months Following TNFi Therapy

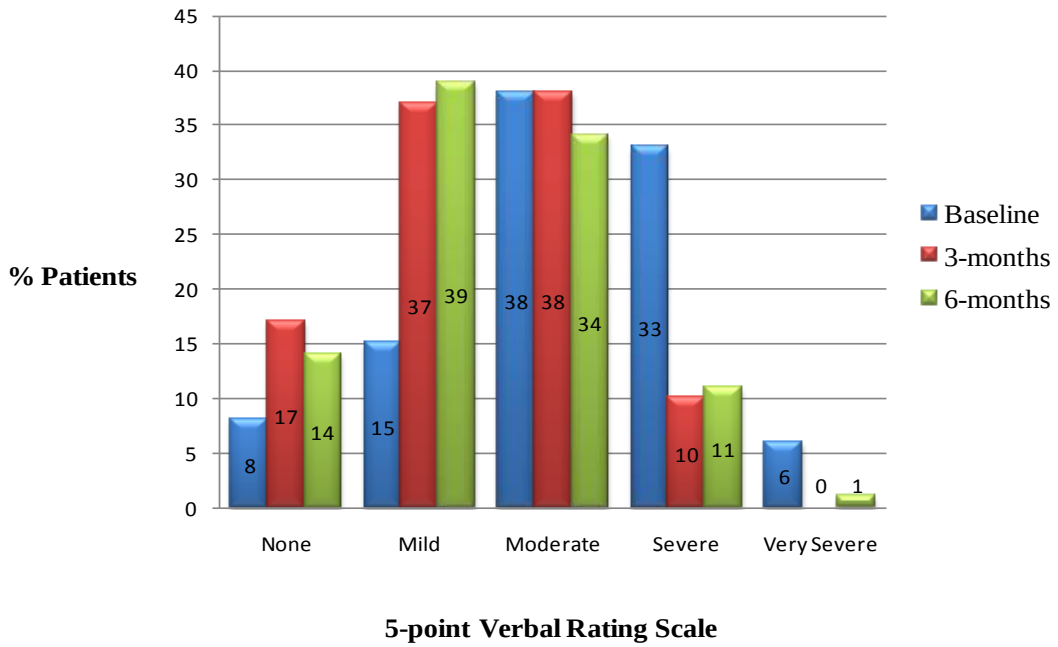
This section summarises fatigue levels in patients with inflammatory arthritis at the three separate times of clinical assessment over a 6-month period following commencement of TNFi therapy.

Levels of fatigue reported by the study cohort were quantified using two separate scales. A single dimension 5-point verbal rating fatigue scale was used to measure levels of fatigue; the multidimensional assessment of fatigue scale, was used to measure four dimensions of fatigue, namely, i) severity, ii) distress, iii) degree of interference with activities of daily living, and iv) timing. These are summarised to give an overall Global Fatigue Index, on a continuous scale.

Figure 5-3 summarises fatigue levels according to the 5-point verbal rating fatigue scale at baseline; and at 3-months and 6 months follow-up. Over 75% of patients reported moderate to severe fatigue levels at baseline. At the 3-months time point the number of patients reporting no fatigue or mild fatigue increased, while reports of severe fatigue noticeably decreased. There were no reports of very severe fatigue at 3-months follow-up. This improvement in reports of fatigue levels was maintained at 6-months follow up; 14% patients experienced no fatigue, 39% patients reported mild fatigue, 34% patients reported moderate fatigue, 11% patients reported severe fatigue and there was one report of very severe fatigue (1%).

Friedman's non-parametric test for related samples was used to test the differences between the rank ordered fatigue levels across the 3-time points. There was a statistically significant difference in the verbal rating scale fatigue scores between the 3 time points: χ^2 df (2) = 31.5; p = 0.001 (significant at 0.01 level). Post-hoc analysis was conducted with the Wilcoxon Signed-Rank tests for pairwise comparisons and Bonferroni correction was applied for multiple comparisons. The initial significance level (0.05) was divided by the number of tests conducted (0.05/3 = 0.0166) (Laerd Statistics 2011).

Figure 5-3: Fatigue levels in patients with inflammatory arthritis at baseline, 3-months and 6-months on the verbal rating scale

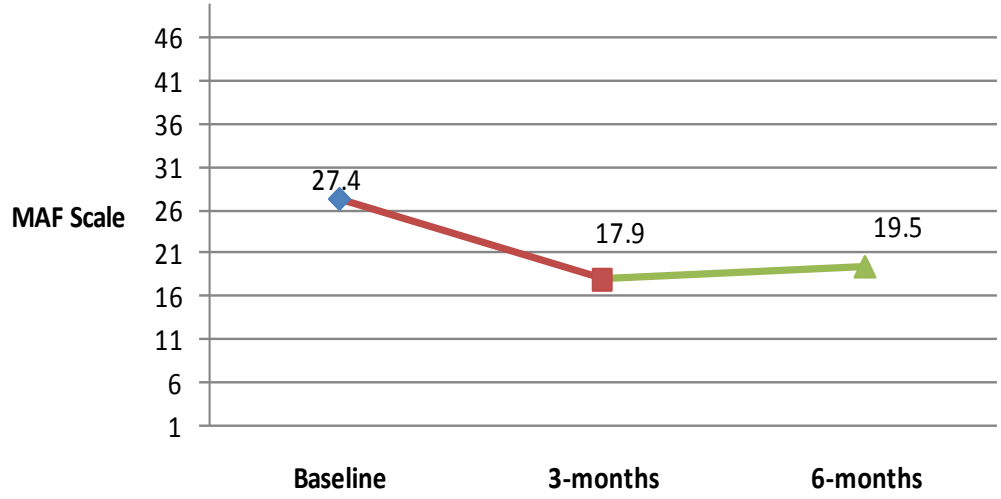


(Assessments: Baseline n=124; 3-months n=109; 6-months n=84)

Ordinal scale fatigue levels improved significantly from baseline to 3-months, ($Z = -5.908$, $p<0.001$). The further improvement observed between 3 and 6 months ($Z = -0.185$, $p=0.853$) failed to reach statistical significance; the mean rank data showed that at 6 months (n=69), there were 18 reports of increased fatigue, and 17 reports of decreased fatigue, and 34 reports of no change in fatigue levels from 3–months. However, the overall improvement from baseline to 6-months was statistically significant ($Z = -4.960$, $p<0.001$), as the early improvements in fatigue were maintained.

The different levels of fatigue reported by patients at each of the time points using the multidimensional assessment of fatigue are presented in Figure 5-4. These are in keeping with the findings on the verbal rating fatigue scale. The mean ± (SD) levels of fatigue measured by the multidimensional scale (scale 1-50) commenced at 27.4 ± 11.1, at baseline. Following treatment with anti TNF therapy multidimensional fatigue scores fell to 17.9 ± 12.2 at 3-months and to 19.5 ±11.5 at 6-months.

Figure 5-4: Multidimensional assessment of fatigue (MAF) levels in patients with inflammatory arthritis at baseline, 3-months and 6-months



(Assessments: Baseline n=130; 3-months n=96; 6-months n=83)

To test the null hypothesis that there was no significant difference between the mean multidimensional fatigue levels at the 3 separate time points, a within subjects one way analysis of variance (ANOVA) was conducted. Post-hoc analysis used Bonferroni adjustment method for multiple testing in the pairwise comparison of the means between the time points. The one-way ANOVA method showed the improvement over time between the three multidimensional scores to be statistically significant, beyond the 0.05 level: $F(2, 118) = 17.14$: $p < 0.001$. However, this is a small effect size as shown by Partial Eta^2 of 0.23 (Cohen 1988; Kinnear and Gray 2009). Pairwise comparisons showed a significant difference between two of the three pairs; baseline and 3-month values ($p < 0.001$) and, baseline and 6-month values ($p < 0.001$). No improvement was observed between 3-months and 6-months. The null hypothesis was therefore rejected as there was a significant improvement in fatigue over time.

In summary, a reduction in fatigue levels across the three time points was demonstrated on both scales following treatment with TNFi therapy. Both scales captured a significant reduction in fatigue from baseline to 3-months and to 6-months. The further change in fatigue levels between the 3-month and 6-month time points on both the 5-point verbal rating scale and the multidimensional scale was found not to reach statistical significance. The size of the effect of TNFi therapy on the variable fatigue was estimated at 23%. These results confirm improvement in both single dimension and multidimensional fatigue levels occurred in parallel with improvement in the core set of outcome measures following TNFi therapy.

5.5 Comparisons between the Measurement Properties of the Verbal Rating Scale and the Multidimensional Assessment of Fatigue Scale

This section examines the comparison between the measurement properties of the single dimensional scale versus the multidimensional scale in the measurement of fatigue in patients with inflammatory arthritis over a 6-month period following commencement of TNFi therapy. Psychometric properties of the respective scales, either not previously reported or considered to be limited in nature (Hewlett *et al.* 2007), were evaluated. Aspects of scale reliability, sensitivity to change following an intervention, validity in measuring fatigue in inflammatory arthritis, and feasibility of use in clinical practice were compared across both scales. The questions asked in this regard, based on published methods are presented in Table 5-6, (Boers *et al.* 1998; Katz 2003; Hewlett *et al.* 2007; Polit and Beck 2010a).

5.6 Reliability of the 5-point Verbal Rating Scale and the Multidimensional Assessment of Fatigue Scale in Inflammatory Arthritis

i) Internal Consistency of the Multidimensional Assessment of Fatigue Scale

The aspect of instrument reliability examined in relation to the multi-item multidimensional assessment of fatigue scale was internal consistency of scale items, using Cronbach's alpha, (Table 5-6). The coefficient alpha was computed for the two subscales as well as the entire scale as it is suggested inflated values can result when computed for an entire scale, that is, a scale composed or 2 or more subscales (DeVon *et al.* 2007). Accepted standards (≥ 0.70 research tools; ≥ 0.90 for clinical tools) were demonstrated for the two subscales, and the entire scale (Trochim 2006; DeVon *et al.* 2007).

Table 5-5: Internal consistency of the multidimensional assessment of fatigue (MAF) scale in patients with inflammatory arthritis prescribed TNFi therapy

	Cronbach's Alpha Coefficient		
MAF Subscales	**Baseline**	**3-months**	**6-months**
Level/Severity	.90	.92	.94
Interference	.88	.93	.90
Global Fatigue Index	.90	.95	.93

(Assessments: Baseline n=130; 3-months n=96; 6-months n=83)

The inter-item correlations of the 15 questions which comprise the multidimensional assessment of fatigue scale-global fatigue index on Cronbach's α was 0.90 at baseline, 0.95 at 3-months and 0.93 at 6-months. These high values are in keeping with previously reported data (Section 4.7.2), and reflect the stability of the multidimensional scale in measuring dimensions of fatigue following treatment initiation (Table 5-5). This aspect of reliability testing is not applicable to single dimension scales such as the verbal rating fatigue scale.

Table 5-6: Application of the verbal rating & multidimensional fatigue scales in inflammatory arthritis: evaluation & comparison of scale psychometric properties

Reliability	**Estimate of the consistency of responses within a scale or results which influences stability of measurements over time: how well items measuring the same construct yield same results**
Study application of concepts of reliability	
Internal Consistency	Extent to which the multi-item MAF scale measures dimensions/traits of the fatigue domain *(Cronbach's α)*
Equivalence/ Parallel Forms	Extent to which two separate instruments measure the same concept: agreement and congruence between results on both scales on repeated measurement *(Kendall's τ-b Correlation Coefficient)* (Trochim 2006; Kinnear and Gray 2009; Polit and Beck 2010a)
Validity	**Expression of the extent scales measure what they are intended to measure**
Study application of concepts of validity	
Construct	Using *correlation coefficients* both scales were indexed for their degree of i) *Convergence* or correlation with other outcomes such as pain and function, ii) *Divergence* or lack of correlation with outcomes such as vigour/vitality, iii) *Factor Analysis* was used to identify clusters of items of the MAF scale to confirm its multidimensionality
Criterion	Comparison between the verbal rating scale and the 'gold standard' MAF scale in the measurement of fatigue in inflammatory arthritis (*Correlation Coefficients)*
Sensitivity	**Estimates of the sensitivity or responsiveness of scales to change following an intervention**
Study application of concept of sensitivity	
Change over time	i) The ability of both scales to detect change in fatigue levels over time following treatment with TNFi therapy was measured statistically using *ANOVA and post-hoc analysis for pairwise comparison.* ii) The sensitivity of the MAF was compared with the sensitivity of the core outcome measures to change over time following an intervention by calculation of the *Standardised Response Mean* (*SRM*) (mean change score divided by the standard deviation of the change score). SRM cannot be calculated using ordinal level data
Sensitivity to change	The comparative sensitivity to change of both scales for a change in the core set of outcome measures was estimated using *Kendall's τ c coefficient* (Section 4.7.5)
Feasibility	**Ease of application of instruments in terms of constraints**
Study application of concept of feasibility	
Time	*Qualitative* evaluation of ease of completion / responder burden of both scales
Financial	Availability of both scales within the public domain
Interpretability	*Qualitative* evaluation of relative ease of scoring and interpretation of scales

Scale Equivalence: Agreement and Congruence between Scales

Equivalence in this context of reliability assessment was concerned with the degree of agreement between the results from both scales in the measurement of fatigue at each clinical assessment (Trochim 2006; Polit and Beck 2010a). The level of agreement and congruence between results on the 5-point verbal rating scale (ordinal data) and the continuous multidimensional assessment of fatigue scale, across the three time points, is presented in Table 5-7. The data were grouped according to the 5 levels on the verbal rating scale for each of the assessment times. The multidimensional scale values (mean ± SD), within these groups shared increasing scores in line with the increasing scores on the verbal rating scale.

Table 5-7: Correspondence between the verbal rating (VRS) scale and multidimensional assessment of fatigue scale (MAF) at each time point

Fatigue Scores	5-Point Verbal Rating Scale (VRS)				
	None n (%)	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**	**Very Severe n (%)**
Baseline VRS (n=124)	10 (8)	19 (15)	47 (38)	41 (33)	7 (6)
MAF* Mean ±SD	9±8.4	18±8.2	27±8.1	35±7.1	40±5.1
3-months VRS (n=95)	16 (17)	33 (37)	36 (38)	10 (10)	
MAF* Mean ±SD	3±3.7	12±5.9	25± 9.4	34±8	
6-months VRS (n=82)	12 (14)	33 (39)	29 (34)	9 (11)	1 (1)
MAF* Mean ±SD	5±4.7	14±6.1	27± 7.0	33±9.0	42

*Multidimensional assessment of fatigue scale range 1-50.

As displayed (Table 5-7), fatigue levels ranked as ‘none’ on the verbal rating scale equated to a mean multidimensional score of <10; mild fatigue was equivalent to a mean multidimensional score of 10<20; moderate fatigue corresponded to a mean multidimensional score of 20<30; severe fatigue equated to a mean multidimensional score of 30<40; and very severe fatigue corresponded to a mean multidimensional score of more than 40. The observed overall trends in agreement between results (Table 5-7), is

representative of the degree of consistency between the two separate instruments in measuring the concept of fatigue, across the 3 time points are summarised in (Table 5-8).

Table 5-8: Summary of correspondence between verbal rating fatigue scale (VRS) and multidimensional assessment of fatigue scale (MAF)

	VRS Ranks				
Mean MAF Scores (Range 1-50)	**None** <10	**Mild** 10<20	**Moderate** 20<30	**Severe** 30<40	**Very Severe** 40<50

Estimate of Equivalence

The measure of agreement between the ranked data on the verbal rating fatigue scale, and the continuous data on the multidimensional fatigue scale, Figure 5-3 and Figure 5-4, was estimated using Kendall's τ b coefficient (Kinnear and Gray 2009). Coefficient values at baseline were r = 0. 736 ($p < 0.001$); at 3-months r = 0.802 ($p < 0.001$); and at 6-month r = 0.696 ($p < 0.001$) (Table 5-9), representing moderate to large agreement between the verbal rating scale and the overall score on the multidimensional scale, at each time point; these were significant beyond the 0.01 level (2-tailed).

ii) Parallel Forms: Consistency of Results between the Verbal Rating Fatigue Scale and the Multidimensional Assessment of Fatigue Scale (MAF)

Equivalency (parallel forms reliability) was also tested between the verbal rating scale and the subscales within the multidimensional scale to test the consistency of results between scales (Trochim 2006). Kendall's τ b statistic for measures of agreement between ranked data was used to test the inter-scale consistency between the verbal rating scale and the two multidimensional subscales; fatigue severity/level and fatigue interference. Correlations coefficients range between 0.546 and 0.746 (Table 5-9), (all were significant at the 0.01 level).

Best correlations were seen between the verbal rating fatigue scale and the multidimensional subscales for i) severity based intensity score, and ii) the overall global fatigue index. The verbal rating scale, which is a severity based scale, was less well correlated with the interference score on multidimensional assessment of fatigue scale, which measures the impact of fatigue on activities. Overall these data highlight the general similarity between the verbal rating fatigue scale and the multidimensional assessment of fatigue scale.

Table 5-9: Correlations between the verbal rating fatigue scale and the multidimensional assessment of fatigue scale:
Intensity score, interference score and global fatigue index at baseline, 3-months and 6-months

MAF Scales	Verbal Rating Scale Kendall's τ b	p-value
MAF Level/Severity (∑ Questions 1-3)		
Baseline (n=124)	0.732**	<0.001
3-months (n=109)	0.746**	<0.001
6-months (n=84)	0.671**	<0.001
MAF Interference Score (Mean ∑ Questions 4-14)		
Baseline (n=124)	0.651**	<0.001
3-months (n=109)	0.546**	<0.001
6-months (n=84)	0.605**	<0.001
MAF Global Fatigue Index (∑ Q1-3+Mean ∑Q4-14 + Q15)		
Baseline (n=124)	0.736**	<0.001
3-months (n=95)	0.802**	<0.001
6-months (n=82)	0.696**	<0.001

** Correlation is significant at the 0.01 level (2-tailed).

This study confirmed the reliability of both scales. The previously reported internal consistency of the multidimensional scale (Belza *et al.* 1993), was upheld for all three subscales. Coefficients ranged between 0.88 and 0.95; these are in keeping with those reported by its developer (Tack 1990a; Belza 1995), and satisfying accepted standards of ≥ 0.90 for clinical tools, and ≥ 0.70 for research tools (DeVon *et al.* 2007). Secondly, the equivalence reliability of both scales in measuring the same attribute was demonstrated. The consistency between the verbal rating scale, and the overall multidimensional scale and

its two subscales (fatigue severity/level and fatigue interference), was supported by moderately high levels of agreement with all, at the three assessment times (coefficient range 0.54-0.80). In summary, estimates of reliability between the verbal rating fatigue scale and the multidimensional assessment of fatigue scale demonstrated a strong level of congruence and agreement, and consistency of results between the scales in measuring the symptom of fatigue in patients with inflammatory arthritis.

5.7 Validity of the 5-Point Verbal Rating Scale and the Multidimensional Assessment of Fatigue Scale in Inflammatory Arthritis

i) *Construct Validity*

Construct validity is the expression of the extent scales measure the construct that they are intended to measure. Aspects evaluated included, convergent and divergent validity, and factor analysis (Table 5-6).

Convergent validity, defined earlier (Table 5-6), of both fatigue scales was previously supported by evidence of a moderate correlation with appropriate outcome measures such as pain and function (Katz 2003; Hewlett *et al.* 2007; Polit and Beck 2010a). The association between the verbal rating scale and pain and function was measured using Kendall's τ b for measures of agreement between ranked and continuous data. Pearson's correlation coefficient was calculated to determine the association between the continuous data from the multidimensional scale and both pain and functional status measured by the HAQ disability index (Table 5-13). The associations between pain and fatigue measured on either scale were moderate and statistically significant, ranging between r = 0.405 and 0.567. The observed associations between both fatigue scales and the HAQ disability index while statistically significant were lower with coefficient values ranging from r = 0.269 and 0.445. All correlations were significant at the 0.01 level (2-tailed).

Divergent validity, defined earlier (Table 5-6), was tested by measuring the association between levels of fatigue measured at 6-months on both scales and (i) the vigour component of the Profile of Mood States (POMS) scale, and (ii) the Self-Efficacy for Other Symptoms Scale. These POMS and self-efficacy data were collected in the second section of this quantitative phase of the study which was confined to a subset of patients with rheumatoid arthritis. The POMS scale, designed to measure mood state, captures elements about energy and vitality within its 'Vigor' scale which may be relevant to the overall fatigue construct. Divergent validity was demonstrated by the negative correlations between the POMS-Vigor Component and both the verbal rating fatigue scale (r = -0.296, p<.013), and the multidimensional scale (r = - 0.239, p< 0.022). Similarly, the Self-Efficacy

for Other Symptoms scale which incorporates questions related to self-management of symptoms including fatigue was indexed for its association with both the verbal rating scales (r=- 0.367, p=0.002) and the multidimensional scale (r=- 0.265, p=.010). All correlations were significant at the 0.05 level (2-tailed) (Kendall's τ b statistic for ranked data). The negative correlations indicate fatigue levels captured on both scales were inversely related to both vigor/vitality levels and patients' perception of their ability to self-manage symptoms other than pain and function. These results highlight the discriminant properties of each fatigue scale.

Factor analysis, defined earlier (Table 5-6), was also used to confirm the construct validity of the multidimensional scale, and to identify clusters of scale items to confirm its claim to measure more than one dimension of fatigue. The 16 item scale was subjected to exploratory factor analysis, using varimax rotation, at each of the time points (Table 5-10).

At baseline three separate factors were identified (Table 5-10); factor 1 (eigenvalue 7.0) explained 44% of the variance, factor 2 (eigenvalue 1.9) explained 12% of variance, factor 3 (eigenvalue 1.4) explained 9% of the variance. Factor 1 represented components related to interference with the daily activities, namely, chores, cooking, bathing and dressing, work and socialising, factor 2 represented items related to interference with physical activity and leisure, factor 3 represented items related to quantity and quality of fatigue - severity, distress, and timing (Table 5-10).

At both the 3-month and 6-month timepoints all items loaded on factor 1 only (eigenvalue 9.1; 57% variance), and (eigenvalue 8.3; 51% variance) explaining over 50% of the variance.

Table 5-10: Factor analyses of multidimensional assessment of fatigue scale items

	Baseline (n=130)			**3-months** (n=96)			**6-months** (n=83)		
Fatigue Item	Factor 1	Factor 2	Factor 3	Factor 1	Factor 2	Factor 3	Factor 1	Factor 2	Factor 3
Degree	.311	.178	.850	.770	.411	-.269	.836	-.088	-.342
Severity	.275	.135	.858	.791	.392	-.141	.819	-.200	-.434
Distress	.480	.190	.640	.824	.103	-.225	.807	-.080	-.328
Interference with*....*									
Chores	.665	.328	.437	.880	-.148	-.139	.862	.147	-.216
Cooking	.635	.341	.309	.847	-.274	-.097	.853	.250	-.024
Bathing	.893	.020	.021	.774	-.518	-.213	.660	.688	-.008
Dressing	.852	.023	.076	.739	-.552	-.216	.529	.773	.023
Work	.504	.173	.216	.585	-.077	.236	.660	.150	.507
Socialise	.562	.464	.372	.863	-.243	-.012	.868	.009	.165
Sexual activity	-.004	.648	.222	.633	.339	.380	.423	-.407	.117
Leisure	.115	.877	.129	.696	.219	.545	.689	-.335	.412
Shopping	.336	.717	.215	.842	-.103	.179	.833	-.088	.190
Walking	.198	.739	.223	.808	-.191	.309	.764	-.016	.296
Exercise	.120	.791	.102	.762	.083	.279	.665	-.405	.321
Timing	.209	.231	.757	.690	.467	-.262	.702	-.334	-.369
Change	-.065	.166	.489	.458	.445	-.323	-.187	.080	.234
Eigenvalue	*7.0*	*1.9*	*1.4*	*9.1*	*1.7*	*1.1*	*8.3*	*1.8*	*1.3*
Explained variance %	*44*	*12*	*9*	*57*	*11*	*7*	*52*	*11*	*9*
Cummulative Variance %		*75*			*75*			*72*	

In summary factors analysis conducted using baseline data showed that the data clustered into 3-main dimensions; 1) interference with activities of daily living, 2) interference with social/leisure/physical activity, 3) fatigue severity and timing. These data support the claim that the multidimensional assessment of fatigue scale measures more than one dimension in the domain of fatigue in inflammatory arthritis. . However, this was not upheld by the 3- and 6-month data, which may be explained by the reduced sample size as opposed to lack of multiple constructs (Table 5-10).

ii) Criterion Validity: Comparison between the Verbal Rating Fatigue Scales and the 'Gold Standard' Multidimensional Assessment of Fatigue Scales

Criterion validity, defined earlier (Table 5-6), of the verbal rating scale was examined against the multidimensional assessment of fatigue scale, at the same time point. The association between the scales was indexed using Kendall's τ b for ranked data (presented earlier (Table 5-9). The measures of agreement between both scales were moderate and statistically significant at each time point; baseline $r = 0.736$; $p < 0.001$; at 3-months $r = 0.802$; $p<.001$; and at 6-months $r=0.696$, $p<0.001$, (Table 5-9). All correlations were significant at the 0.01 level (2-tailed); the 3-month and 6-month coefficients reached the desirable level of 0.70 (Polit and Beck 2010a). These correlations between the scales support the concept of criterion validity in relation to the verbal rating scale in the measurement of fatigue in inflammatory arthritis.

In summary, this study provides new evidence in relation to various aspects of validity for both the verbal rating and multidimensional assessment of fatigue scales. Firstly, evidence of face validity for the verbal rating scale, and both face and content validity for the multidimensional scale in patients with rheumatoid arthritis and psoriatic arthritis following an intervention was demonstrated. Secondly, the construct validity for both fatigue scales was observed in terms of convergence with pain and function, and divergence from vigor, and self-efficacy for other symptoms. Furthermore, the multidimensionality of the multidimensional assessment of fatigue scale was supported on factor analysis. Thirdly, correlations between the both scales support the concept of criterion validity in relation to the verbal rating scale in the measurement of fatigue in inflammatory arthritis

5.8 Sensitivity to Change of the 5-point Verbal Rating Scale, and the Multidimensional Assessment of Fatigue Scale, in Inflammatory Arthritis

For the purpose of scale comparison the question of the discrimination property of sensitivity to change of both measurement scales was examined (Boers *et al.* 1998). Firstly, change over time following an intervention (responsiveness) was measured and secondly, the sensitivity to change of the multidimensional assessment of fatigue scale relative to that of the core set outcomes measures was calculated using the standardised response mean (SRM) (Walters and Brazier 2003). Calculation of the SRM is not possible with ordinal scale data. A third test examined the comparative sensitivity to change of each of the fatigue scales for a change in the core set variables at both time points (Wolfe 2004).

i) Change Over Time

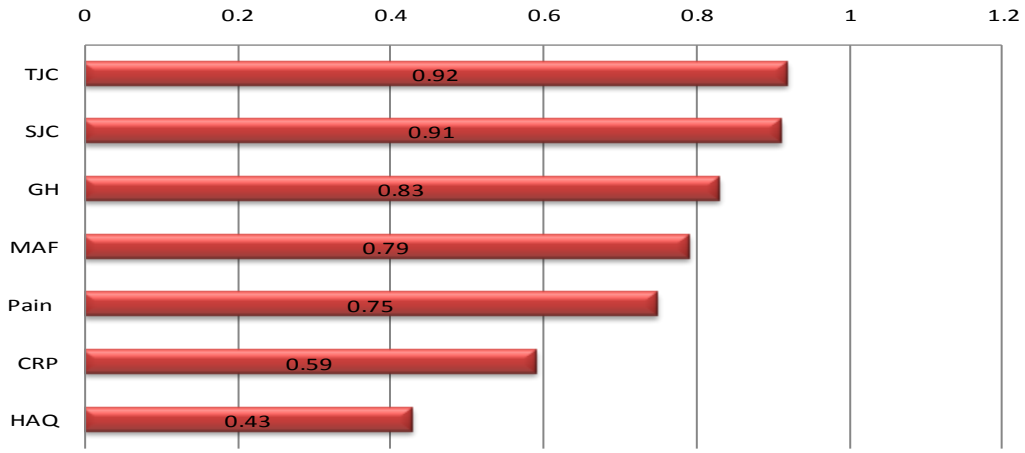
Difference between Mean Scores over Time

A reduction in fatigue levels across the three time points was demonstrated on both scales. The capacity of both instruments to measure change statistically (Walters and Brazier 2003), was demonstrated firstly in the verbal rating scale using non-parametric *Wilcoxon Rank* sign test χ^2 df (2) = 31.5; p= 0.001 (significant at 0.01 level) (Figure 5-3); and also in the multidimensional scale using the parametric *ANOVA F* (2, 118) = 17.04: p < 0 001, as presented earlier, (Figure 5-4). The one-way ANOVA method showed the improvement over time between the three multidimensional scores to be statistically significant, beyond the 0.05 level: F (2, 118) = 17.14: p <0.001 (Table 5-3). Both scales captured a significant reduction in fatigue levels between baseline and 3-months, and baseline and 6-months. The change in fatigue levels measured between the 3-month and 6-month time points was found not to reach statistical significance on either scale. These results show that the performance of both scales in relation to sensitivity to change over time was similar at all time points.

ii) Sensitivity to Change of the Multidimensional Assessment of Fatigue Scale Relative to the Core Set of Outcome Measures

The responsiveness of the multidimensional scale to change following treatment was determined by measuring its sensitivity to change over time and comparing it with that of the core set outcome measures through calculation of the standardised response mean (SRM) (Walters and Brazier 2003), at both the 3-months and the 6-month time point. The SRM is calculated as the mean change score divided by the standard deviation of the change scores. This measure permitted a comparison to be made between the sensitivity to change of the multidimensional fatigue scale and the sensitivity of the core outcome measures. It is suggested that SRM's of 0.2 - 0.5 should be regarded as small, 0.5 - 0.8 as moderate, and > 0.8 as large (Cohen 1988).

Figure 5-5: Standardised response means at 3-months following commencement of TNFi therapy



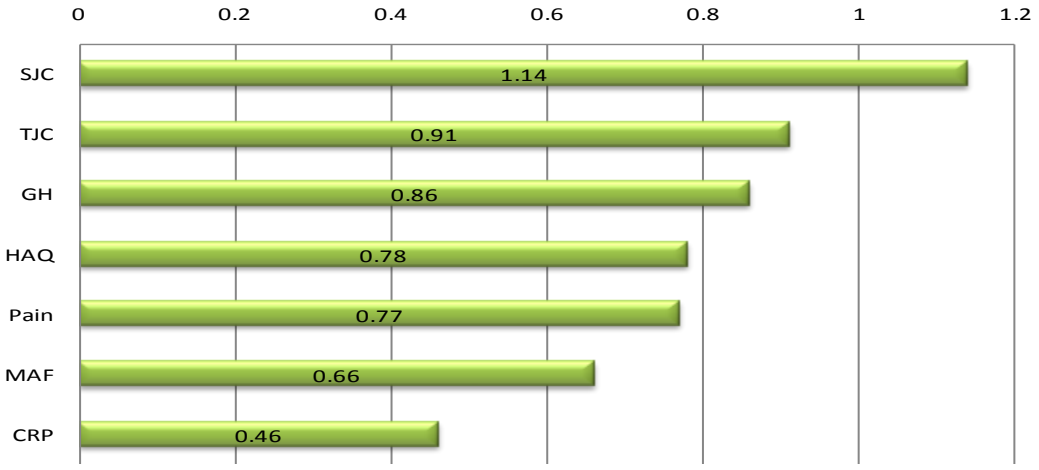
SJC: Swollen Joint Count 28 n=107; TJC: Tender Joint Count 28 n=107; Pain VAS: Pain visual analogue scale n=106; GH: Patient Global Health n=108; HAQ: Health Assessment Questionnaire disability index n=102: CRP; C-Reactive protein n=102: MAF: Multidimensional Assessment of Fatigue Scale n=95

At 3-month follow-up the sensitivity to change of the multidimensional assessment of fatigue scale relative to that of the core set outcome measures according to the SRM is displayed in Figure 5-5. Moderate to large effect sizes were demonstrated for all variables with the exception of a small effect size for the HAQ disability index. Fatigue was ranked fourth after tender joint count, swollen joint count and global health in terms of its ability to

detect change over time confirming its comparable sensitivity to change with that of the conventional core outcome measures.

At the 6-month time point fatigue was ranked sixth after swollen joint count, tender joint count, global health, HAQ disability index and pain in its sensitivity to detect change from baseline to the 6-month time point. Moderate to large effect sizes were demonstrated for six of the seven variables examined; the exception was C-reactive protein which demonstrated a small effect size as seen in Figure 5-6. These results confirm the comparable sensitivity to change of the multidimensional assessment of fatigue scales with that of the conventional core outcome measures.

Figure 5-6: Standardised response means at 6-months following commencement of TNFi therapy



SJC: Swollen Joint Count 28 n=82; TJC: Tender Joint Count 28 n=82; Pain VAS: Pain visual analogue scale n=83; GH: Global Health n=85; HAQ: Health Assessment Questionnaire-disability index n=79: CRP; C-reactive protein n=85: MAF: Multidimensional Assessment of Fatigue Scale n=85.

iii) Comparative Sensitivity of Change in Fatigue Scales to Change in Core Set Outcome Measures

The comparative sensitivity to change of each of the fatigue scales for a change in the individual core set outcome measures and the composite DAS28 score was assessed using Kendall's τ _c (Wolfe 2004). This can be intrepreted in terms of percentage agreement in the sense that, for example, at 3-months, an increase in the verbal rating scale (coefficient 0.10), and the multidimensional scale (coefficient r=0.24), are 10% and 24%, respectively, more likely to be associated with an increase, than a decrease, in the HAQ-disability index at 3-months (Table 5-11) (Wolfe 2004; StatSoft 2011).

Table 5-11: Comparison of the verbal rating fatigue scale (VRS) and the multidimensional assessment of fatigue scale (MAF) with core set variables at 3- and 6-months

	Kendall's τ c coefficient	p-value	Kendall's τ c coefficient	p-value
Variable Difference (Δ)	**3-months**		**6-months**	
Δ Swollen Joint Count				
VRS 10 (n=106), (81)	.032	.646	-.051	.572
Δ MAF (n=90), (53)	.053	.439	.041	.681
Δ Tender Joint				
VRS (n=106), (81)	.080	.223	.094	.266
Δ MAF (n=90), (53)	.067	.356	-.027	.772
Δ Pain				
VRS (n=105), (82)	.124	.080	.031	.718
Δ MAF (n=90), (53)	.279	<.001*	.070	.413
Δ Global Health				
VRS (n=107), (84)	.050	.501	.012	.896
Δ MAF (n=91), (54)	.292	<.001*	.184	.029*
Δ HAQ				
VRS (n=101), (78)	.103	-.162	-.029	.746
Δ MAF (n=86), (49)	.240	<.001*	.108	.283
Δ CRP				
VRS (n=105), (84)	-.018	.777	-.025	.765
Δ MAF (n=87), (55)	.033	.663	-.149	.111
Δ DAS28				
VRS (n=98), (78)	.051	.464	.125	.152
Δ MAF (n=82), (51)	.236	<.001*	-.078	.430

Δ differences in variable score between baseline and assessment time point.

The data used were the change scores from baseline to 3-months, and baseline to 6-months for both fatigue scales (Table 5-11). At 3-months the multidimensional assessment of

fatigue scale, and not the verbal rating scale, was more sensitive ($p < 0.001$) to change in pain, global health, the HAQ-disability index, and DAS28. At 6-months the multidimensional assessment of fatigue scale showed sensitivity to patient global health variable ($p = 0.029$), only. These results demonstrate that the verbal rating fatigue scale is less sensitive to change in the core outcome measures than the multidimensional assessment of fatigue scale.

To summarise, the ability of both the verbal rating fatigue scale and the multidimensional assessment of fatigue scale to detect clinically relevant change was demonstrated. Firstly, a statistically significant difference between mean fatigue levels at baseline and both 3-months, and 6-months follow up was demonstrated on both scales. Secondly, the magnitude of this change (effect size) on the multidimensional scale was seen when compared with the effect size of the core set of outcome measures. Fatigue was ranked fourth after tender joint count, swollen joint count and global health in terms of its ability to detect change 3-months post baseline, at 6- months post baseline it was ranked sixth, being superior to the laboratory measure CRP, only. Thirdly, assessment of the comparative sensitivity to change of each of the fatigue scales in the detection of a change in each of the core set outcome measures highlighted the superiority in terms of responsiveness of the multidimensional assessment of fatigue scale. At 3-months the multidimensional assessment of fatigue scale, and not the verbal rating scale, was more sensitive to change in pain, global health, the HAQ disability index and DAS28. At 6-months the multidimensional assessment of fatigue scale showed sensitivity to patient global health variable, only.

This longitudinal study confirms that both the short form and long form scales are equally sensitive to change over time. Knowledge that the short form scales is sensitive to change supports its use in situations where minimal responder and administrator burden is imperative, such as pressurised clinical settings. This confirms short form scales are suitable for screening and quantification. Where more in-depth knowledge on the symptom experience of fatigue in relation to other variables is required the multidimensional scale was shown to be more responsive. This suggests that the multidimensional scale is the instrument of choice for comprehensive assessment of interventions in the management of this complex phenomenon.

5.9 Clinical Characteristics of and the Relationship between Fatigue and the Conventional Core Outcome Measures

A major aim of this study was to examine the clinical characteristics of fatigue and the relationship between fatigue and the six core outcome measures in order to determine contributory factors to fatigue (Table 5-12).

Table 5-12: Correlations between patient demographics and fatigue at baseline, 3-months and 6-months

Patient Demographics (n (MAF), (VRS)	Spearman's rho	p-value Sig.(2-tailed)	Spearman's rho	p-value Sig.(2-tailed)
	MAF Scale		*Verbal Rating Scale*	
Gender				
Baseline (n=130), (124)	.132	.133	.157	.083
3-months (n=96), (109)	.008	.939	.034	.727
6-months (n=83), (84)	.196	.076	.179	.104
Diagnosis				
Baseline (n=130), (124)	.030	.130	.082	.368
3-months (n=109)), (84)	-.029	.778	.016	.725
6-months (n=83)), (84)	-.083	.456	-.039	.014*
Rheumatoid Factor				
Baseline (n=130), (124)	.024	.780	-.028	.756
3-months (n=96)), (109)	.069	.502	-.020	.838
6-months (n=83)), (84)	-.237	.031*	-.226	.038*
Disease Duration				
Baseline (n=128),(122)	-.012	.895	.039	.671
3-months (n=95)), (82)	.047	.651	-.005	.855
6-months (n=81)), (82)	-.039	.728	-.079	.479
Ever Failed DMARD				
Baseline (n=130)), (124)	-.164	.239	-.006	.946
3-months (n=96)), (109)	.013	.900	.085	.378
6-months (n=83)), (84)	.092	.408	.085	.445
Ever Failed Biologic				
Baseline (n=128)), (122)	-.007	.938	.066	.477
3-months (n=94)), (107)	-.021	.838	.034	.726
6-months (n=83), (82)	.140	.211	.076	.495
Current Smokers				
Baseline (n=114)), (108)	-.187	.047*	-.056	.565
3-months (n=82)), (95)	-.158	.155	-.072	.487
6-months (n=78)), (79)	.064	.580	.023	.838

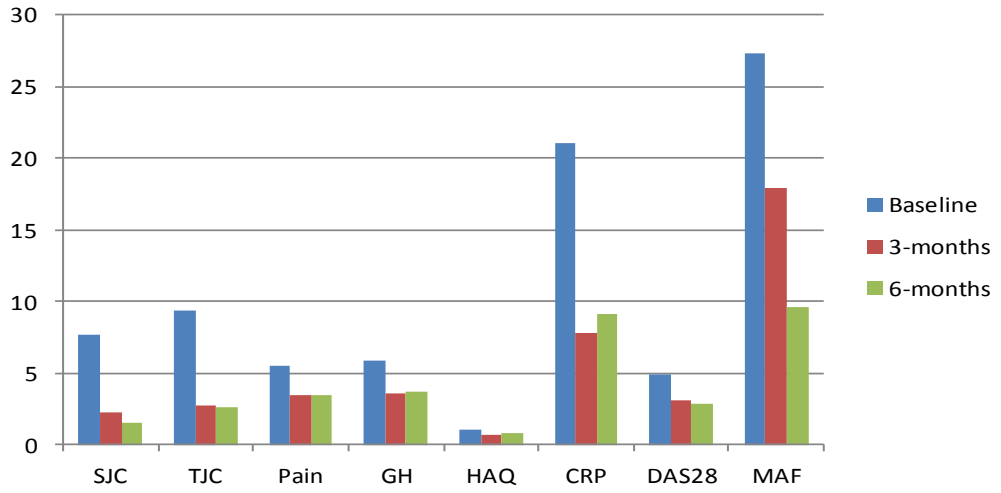
*Correlation is significant at the 0.05 level (2-tailed). DMARD- disease modifying anti-rheumatic drugs.

The extent to which fatigue was explained by other variables such as patient demographics, and clinical disease characteristics was estimated using measures of association; factor analysis was used help clarify its status as either an inflammatory (process) or health status (outcome) measure.

Firstly, potential contributory factors were examined by exploring the relationship between both fatigue scales at the 3-time points, and patient baseline demographics; Table 5-12. Baseline demographics were shown not to exert any major significant influence on fatigue.

The changes in the multidimensional assessment of fatigue scales along with those of the core set outcomes across the three time points are presented in Figure 5-7.

Figure 5-7: Changes in the core set outcome measures at the three timepoints



SJC: Swollen Joint Count 28. TJC: Tender Joint Count 28. Pain VAS: Pain visual analogue scale. GH: Patient Global Health; HAQ: Health Assessment Questionnaire-disability index: CRP; C- Reactive protein: DAS28; Disease Activity Score 28. MAF, GFI: Multidimensional Assessment of Fatigue Scale, Global Fatigue Index

As previously presented (Figure 5-2 and Table 5-2) changes measured in the core set outcomes at 3-months and 6-months follow–up were shown to be statistically significant and representative of a clinical improvement in disease status following treatment with TNFi therapy. Figure 5-7 demonstrates how fatigue levels, captured by the multidimensional assessment of fatigue scale, improved in parallel with the core set

outcome measures following treatment. The statistical significance of this improvement was already presented in Section 5.4.

The high scores obtained on the conventional disease outcome measures prior to commencement of TNFi therapy are representative of an active disease state in patients with inflammatory arthritis. Fatigue, an additional outcome measure, also demonstrated high levels at baseline suggesting that fatigue is also an inflammatory variable. Levels of fatigue fell in parallel with those of the conventional outcome measures following treatment with TNFi therapy, captured at 3-month and 6-months follow-up.

Correlations

Having established that fatigue and the core set outcome measures changed significantly over time, and that these variables were little influenced by demographic characteristics, the relationship between both fatigue scales and the core set of outcome measures was examined. The relationships between the outcomes measured on a continuous scale were calculated using Pearson's r statistic, while the relationship between the verbal rating scale (ordinal data) and the core outcomes was measured using the Kendall's τ statistic.

All but 3 of the 42 associations tested demonstrated comparable significant correlations (Table 5-13). A moderately strong relationship was seen between fatigue and each of the clinical outcome measures at every time point. The weakest relationship seen was between fatigue, and the acute-phase reactant; C-reactive protein. This lack of correlation between fatigue and acute phase markers either CRP and ESR has been identified previously (Rasker 2009). These measures of association demonstrated consistency of results between the verbal rating scale and the multidimensional scale at all timepoints. Moreover, they confirm significant associations between fatigue and both patient reported and clinician reported outcome measures during different disease states.

Table 5-13: Relationship between the verbal rating fatigue scale and the multidimensional assessment of fatigue scale and the core set variables

Fatigue and the Core Set Variables (n (MAF), (VRS)	r	p-value Sig.(2-tailed)	Kendall's τ b	p-value Sig.(2-tailed)
	Multidimensional Scale		***Verbal Rating Scale***	
Verbal Rating Scale	***Kendall's τ b***			
Baseline (n=124)	.587**	<.001	1	-
3-months (n=95)	.691**	<.001	1	-
6-months (n=82)	.696**	<.001	1	-
Swollen Joint Count	**Pearson's r**			
Baseline (n=125), (n=120)	.043	.634	-.028	.689
3-months (n=95)), (108)	.359**	<.001	.229**	.004
6-months (n=81)), (82)	.304**	.006	.230*	.014
Tender Joint				
Baseline (n=130), (120)	.199*	.026	.099	.160
3-months (n=95)), (108)	.414**	<.001	.280**	<.001
6-months (n=81)), (82)	.316**	.004	.221*	.017
Pain				
Baseline (n=124), (121)	.410**	<.001	.409**	<.001
3-months (n=96)), (108)	.567**	<.001	.405**	<.001
6-months (n=83)), (84)	.518**	<.001	.406**	<.001
Global Health				
Baseline (n=126)), (122)	.416**	<.001	.429**	<.001
3-months (n=96)), (109)	.518**	<.001	.454**	<.001
6-months (n=83)), (84)	.621**	<.001	.459**	<.001
HAQ- Disability Index				
Baseline (n=125)), (121)	.445**	<.001	.339**	<.001
3-months (n=90)), (102)	.333*	<.001	.291**	<.001
6-months (n=79)), (79)	.338**	.002	.269**	.003
C-Reactive Protein				
Baseline (n=126)), (121)	-.167	.061	-.014	.826
3-months (n=90)), (102)	.223*	.034	.109	.183
6-months (n=80)), (81)	.119	.294	.083	.371
Disease Activity Score 28				
Baseline (n=120)), (116)	.217*	.017	.125	.078
3-months (n=90)), (103)	.586**	<.001	.380**	<.001
6-months (n=79)), (80)	.503**	<.001	.314**	<.001

HAQ-health assessment questionnaire – disability index **Correlation is significant at the 0.01 level (2-tailed). *Correlation is significant at the 0.05 level (2-tailed).

Factor analysis

The final test conducted in the exploration of the characteristics of, and relationship between, fatigue and the core outcome measures was factor analysis. This statistical procedure is a method used to either identify and group together, or to distinguish, different outcome measures of some underlying attribute (Polit and Beck 2010a). Exploratory factor analysis, using varimax rotation, was undertaken in order to detect the existence of any structure in the inter-relationship between fatigue and the core set variables. The question asked was does fatigue along with any of the core set outcome measures represent some underlying or distinguishing attribute in the assessment of outcome in inflammatory arthritis? The eigenvalue of each factor is an estimate of the variance of all the tests (variables) explained by the factor. From this the explained variance (%) can be calculated by dividing the eigenvalue by the number of tests and multiplying by 100 (eigenvalue 2.8/7*100=41%). For example, at baseline, 41% of the total variance in all the tests is explained by factor 1 (Table 5-14).

Table 5-14: Factor analysis of fatigue and core set variables

	Baseline n=116			**3-months** (n=84),		**6-months** (n=75)	
Variable	Factor 1	Factor 2	Factor 3	Factor 1	Factor 2	Factor 1	Factor 2
GH	.856	.127	.093	.773	.097	.879	.223
Pain	.831	.075	-.052	.841	.115	.828	.323
MAF	.699	.067	-.289	.737	.277	.809	.103
HAQ	.643	.441	.192	.639	-.111	.665	.127
SJC	.079	.891	-.025	.668	-.049	.310	.681
TJC	.174	.875	-.060	.636	.034	.373	.755
CRP	-.039	-.047	.970	.033	.972	-.022	.777
Eigenvalue	*2.8*	*1.2*	*1*	*3.2*	*1*	*3.5*	*1*
Explained variance %	*41*	*18*	*15*	*45*	*14*	*50*	*16*
Cummulative Explained %	*65*			*59*		*66*	

SJC: Swollen Joint Count 28. TJC: Tender Joint Count 28. Pain VAS: Pain visual analogue scale. GH: Patient Global Health; HAQ: Health Assessment Questionnaire disability index: CRP; C-reactive protein. MAF, GFI: Multidimensional Assessment of Fatigue Scale, Global Fatigue Index.

Three factors were identified at baseline. Factor 1 identified components related to patient reported outcomes (pain, global health, functional status according to the HAQ disability index, (eigenvalue 2.8; explained variance 41%). Factor 2 represented clinician derived/reported outcomes (swollen joint and tender joint count), (eigenvalue 1.2; variance 18%). Factor 3 represented the laboratory measure of inflammation, (eigenvalue 1; explained variance 15%). This analysis shows that these 3 factors identified accounted for over 74% of the variance. Two factors were identified at 3-months. Factor 1 represented a combination of the patient reported and clinician reported outcomes, (eigenvalue 3.2; explained variance 45%); factor 2 represented the laboratory measure of disease outcome (eigenvalue 1; explained variance 14%). Similarly, two factors were identified at 6-months. Factor 1 represented patient reported outcomes (eigenvalue 3.5; explained variance 50%); factor 2 represented the combination of clinician reported outcomes and laboratory measure of disease activity (eigenvalue 1; explained variance 16%). Therefore the analysis shows that the combined factors identified accounted for over 59% of the total variance at 3-months and 66% at 6-months follow-up.

Three separate attribute clusters were identified: patient reported outcomes, clinician derived outcomes and laboratory derived outcomes. Fatigue consistently grouped with pain, global health, and the HAQ-disability index. Swollen joint count and tender joint count represent the clinically derived measures. The biochemical measure of the acute-phase reactant C-reactive protein stands as a single factor highlighting the distinctive nature of this objective non-specific measure of inflammation. In summary fatigue along with the outcomes of pain, global health and the HAQ-disability index distinguish themselves as patient reported outcomes distinct from the clinician or biochemically derived measures of outcome in inflammatory arthritis.

In summary, baseline demographics were shown not to exert any major significant influence on fatigue, regardless of the scale used. Fatigue along with the outcomes of pain, global health and the HAQ-disability index distinguish themselves as patient reported outcomes distinct from the clinician or biochemically derived measures of outcome in inflammatory arthritis. The findings suggest that the explained characteristics of fatigue are more likely attributed to aspects of pain, global health status and function as distinct from clinical and biochemical disease outcome measures.

5.10 Clarification of the Unique Contribution of Fatigue in the Assessment of Outcome in Patients with Inflammatory Arthritis

Study objectives next focused on the further clarification of both the explained and unexplained contribution made by fatigue to the assessment of outcome in patients with inflammatory arthritis by exploring explained elements of fatigue. The question of whether fatigue can be fully explained by the core set variables or if fatigue contributes additional and independent (unique) information to the assessment of outcome in inflammatory arthritis was addressed in three stages: -

i) Determination of the predictive relationship between fatigue and the core set variables at time of assessment (using absolute scores at each timepoint),
ii) Determination of the predictive relationship between changes in fatigue, and changes in the core set variables, following TNFi therapy (using change scores between baseline and timepoint),
iii) Determination of the explained and unexplained variance in fatigue, and the core set variables in inflammatory arthritis (using change scores between baseline and timepoint (Δ)).

i) Determination of the predictive relationship between fatigue and the core set variables

Univariate Regression Analysis

Firstly, to help clarify the predictive aspect of association between fatigue and the individual core set variables simple linear regression analysis was undertaken. Results are presented in Table 5-15. Data from the 3-separate time points were used, the multidimensional assessment of fatigue scale (continuous scale) were taken as the dependent variable and each of the core set outcome measures were taken in turn as the independent variable. Diagnostic analysis confirmed the model assumption of normal distribution of the chance variation (Appendix 15).

Subtle differences were seen between the results across the three time points; Table 5-15. At baseline, patient reported outcomes explained the greatest variance in fatigue; with the following effect size values (R^2, known as the coefficient of determination); HAQ-disability index 20%; global health, 17%; and pain, 17%; these represent a large effect size, (< 1% small; 1-10%, medium; >10%, large) (Cohen 1988; Kinnear and Gray 2009). Swollen joint count and CRP failed to reach statistical significance.

Table 5-15: Univariate linear regression analysis of multidimensional fatigue scale and core set variables at baseline, 3-months, and 6-months

Variable	Coefficient β	SE(β)	t-value	p-value	R^2 (%)
Baseline n=116					
HAQ(n=125)	7.35	1.33	5.50	<.001*	.20 (20)
GH (n=125)	2.05	.40	5.09	<.001*	.17 (17)
Pain (n=124)	2.10	.42	4.96	<.001*	.16 (17)
TJC (n=125)	0.28	.13	2.25	.026*	.04 (4)
SJC (n=125)	0.08	.16	0.47	.634	.00 (0.2)
CRP (n=126)	-0.07	.04	-1.88	.061	03 (3)
3-months n=84					
Pain (n=96)	3.04	.45	6.83	<.001*	.33 (33)
GH (n=96)	2.70	.46	5.87	<.001*	.27 (27)
TJC (n=95)	1.23	.28	4.38	<.001*	.17 (17)
SJC (n=95)	1.61	.43	3.71	<.001*	.13 (13)
HAQ (n=90)	5.21	1.58	3.31	.001*	.11 (11)
CRP (n=90)	0.26	.12	2.14	.034*	.05 (5)
6-months n=75					
GH (n=83)	3.41	.48	7.12	<.001*	.39 (39)
Pain (n=83)	2.82	.52	5.44	<.001*	.27 (27)
HAQ (n=79)	5.75	1.83	3.14	.002*	.11 (11)
TJC (n=81)	0.72	.24	2.96	.004*	.10 (10)
SJC (n=81)	1.46	.52	2.83	.006*	.09 (9)
CRP (n=80)	0.08	.07	1.05	.294	.01 (1)

SJC: Swollen Joint Count 28. TJC: Tender Joint Count 28. Pain VAS: Pain visual analogue scale. GH: Patient Global Health; HAQ: Health Assessment Questionnaire-disability index: CRP; C-reactive protein. MAF, GFI: Multidimensional Assessment of Fatigue Scale, Global Fatigue Index. *Correlations is significant at 0.01 level (2-tailed); **Correlations is significant at 0.05 level (2-tailed).

The largest effect sizes seen at 3-months were a combination of both patient reported and clinician derived variables pain, R^2 = 33%; global health, R^2 = 27%; tender joint count, R^2 = 17%; swollen joint count, R^2 = 13%, representing large effect sizes. The predictive relationship with all variables reached statistical significance. At the 6 months time point the strongest predictors of fatigue on univariate analysis were global health, R^2 = 39%;

pain, R^2 = 27%; and HAQ, R^2 = 11%; the only variable not to reach statistical significance was the acute phase reactant-CRP.

Multiple Regression Analysis

Secondly, the predictive aspect of association between fatigue and the set of variables (the core set) was examined. Multiple regression analysis (backward deletion) was the appropriate technique used to determine how much variation in fatigue (dependent variable) can be estimated from two or more variables, in this case, the core set variables (independent variables); all independent variables were included in the regression model initially and non-significant predictors removed one at a time in a stepwise manner (Kerr *et al.* 2002). This permitted conclusions to be drawn regarding the relative importance of the set of core variables in the explanation of fatigue. Data used were the absolute values on each of the outcome measures at each of the 3 time points.

Table 5-16: Multiple regression analysis# of fatigue and the core variables at baseline, 3-months, and 6-months

Variable (absolute score)	**β Coefficient**	**SE(β)**	**t-value**	**p-value**	**R^2 (%)**
Baseline (n=116)					
HAQ	4.92	1.49	3.28	.001	.28 (28)
GH	1.57	0.47	3.32	.001	
CRP	-.086	0.03	-2.61	.010	
3-months (n=84)					
Pain	2.39	0.47	5.08	<.001	.37 (37)
TJC	0.68	0.25	2.65	.010	
6-months (n=75)					
GH	3.56	0.44	8.06	<.001	.46 (46)

HAQ Health Assessment Questionnaire disability Index; GH Global Health. CRP C-Reactive Protein, TJC Tender Joint Count. # Backward deletion technique

All of the core set variables were included in the models, even those not significant on univariate analysis; this is recommended when the objective is to explore the complex interrelationships among a set of variables (Altman 1999) (Appendix 15). The guideline of 50 cases minimum plus eight cases for each variable was taken to support statistical analysis with six independent variables (core outcomes) (Tabachnick and Fidell 2001).

At baseline a significant relationship existed between the dependent variable fatigue and the core set of independent variables: F (6, 109) = 8.653; p = <0.001. The individual variables which made the most significant contribution to explaining 28% of fatigue (R^2) were a combination of HAQ-disability index, global health, and CRP.

At 3-months a significant relationship existed between the dependent variable fatigue and the core set of independent variables: F (6, 77) = 9.520; p = <0.001; the variables which made a significant contribution in the final model were pain and tender joint count explaining 37% of the fatigue variance.

At 6-months while a significant relationship existed between the dependent variable fatigue and the core set of independent variables: F (6, 68) = 10.862; p = <0.001 the only significant variable in the final model was global health, which explained 46% of the variance in fatigue (Table 5-16).

ii) Determination of the predictive relationship between changes in fatigue, and changes in the core set variables, following TNFi therapy.

In this analysis the outcome of interest was change in fatigue values at 3-months, and at 6-months; use of the change score controls for within-patient correlation (Altman 1999). The relationships between change (Δ) in multidimensional fatigue levels from baseline (commencement of TNFi therapy) and changes in the six core outcome measures were examined. Again multiple regression analysis (backward deletion technique) was employed using the Δ variables at both the 3 and 6-month time points.

In the final model at 3-months (Table 5-17), a significant relationship existed between the dependent variable Δfatigue and the Δcore set of independent variables: F (6, 68) = 2.948; p = < 0.012. Within this model the two independent variables that made a statistically significant contribution to the prediction of Δfatigue were ΔHAQ-disability index (t=2.74, p=.008), and Δglobal health (t=2.14, p=0.035), explaining 15% (adjusted $R^{2.}$ =0.15).

Table 5-17: Multiple regression analysis*of Δfatigue and the Δcore set outcomes measures at 3-months

ΔVariables (n=75) *(change, 0-3 months)*	**β-coefficient**	**s.e.(β)**	**t-value**	**p-value**	**R^2 (%)**
ΔHAQ	5.57	2.1	2.45	.008	.
ΔGH	1.07	0.5	2.1	.035	15 (15)

HAQ Health Assessment Questionnaire-Disability Index. GH Global Health.* Backward deletion technique

Findings from the final change model at 6-months are noteworthy. Using the change data at 6-months the multiple regression models found that the overall relationship between the dependent variable (Δfatigue) and its predictors (Δcore set of independent variables) was not significant: F = (6, 8) 6.45; p = < 0.694, explained variance of only 5% (adjusted R^2-0.051).

There was no significant relationship between change from baseline in fatigue and change in the core set variables at 6-months.

iii) Determination of the explained and unexplained variance in fatigue and the core set variables in inflammatory arthritis

The purpose of this stage was twofold 1) to calculate the size of the unexplained or independent (unique) contribution of fatigue to the assessment of outcome in inflammatory arthritis, and 2) to compare the magnitude of this contribution to the respective contributions made by the core set variables. The data used were the change in the values (Δ) at 3-months, and at (Δ) 6-months, of fatigue and the six core set variables. Each of these seven Δ variables were taken in turn as the dependent variable and regressed against the 6 remaining variables to calculate the explained variance ($R^{2)}$). This gave a measure of variation in, i) fatigue and, ii) in each of the core set variables, that could be explained by the variation in all of the other 6 outcome measures. To provide an estimate of the unexplained variance, subtraction of R^2 from 1 gave the unexplained variance or independent contribution made by the dependent variable. This was repeated for each of the variables (Kirwan *et al.* 2007).

Table 5-18: Regression of Δ fatigue and the Δ core set variables at 3- months

Measure (Δ 0-3 months) (n=75)	R multiple correlation	R^2 % explained variance,	$1-R^2$ %unexplained variance	F (p) overall model significance
MAF	0.46	0.21 (21)	0.79 (79)	2.984 (.012)
CRP	0.11	0.01 (01)	0.99 (99)	0.136 (.991)
HAQ	0.41	0.17 (17)	0.83 (83)	2.281 (.046)
Pain	0.60	0.36 (36)	0.64 (64)	6.407 (<.001)
Swollen joint count	0.63	0.39 (39)	0.61 (61)	7.281 (<.001)
Tender joint count	0.63	0.39 (39)	0.61 (61)	7.271 (<.001)
Global Health	0.62	0.38 (38)	0.62 (62)	7.064 (<.001)

HAQ, health assessment questionnaire-disability index; MAF, multidimensional assessment of fatigue-global fatigue index; CRP, C-reactive protein. R = multiple correlation coefficient with changes in the linear combination of the rest of the measures. R^2 = coefficient of determination or explained variance; proportion of variance in the measure associated. $1-R^2$ = proportion of variance not predicted by the rest of the measures.

The results from the 3-month change data are presented in Table 5-18. Fatigue variance was largely unexplained (79%) by the core set variables, evidence that measuring fatigue provides a unique contribution to the assessment of outcome in inflammatory arthritis. The only variables which made a higher unexplained contribution were HAQ (83%) and CRP (99%). The measures that made the lowest independent (unexplained) contribution to assessment of outcome at 3-months were swollen and tender joint count (61%).

Similarly, at 6-months Δ fatigue made the considerable independent contribution to the assessment of outcome in inflammatory arthritis with 91% of its variance being unexplained by the core set variables, with Δ CRP being the only other variable with a higher unexplained variance (94%); this shows that both of fatigue and CRP provide information that overlaps with that of the core set outcome measures and, moreover, both provide a comparable amount of information about outcome in inflammatory arthritis, that does not overlap with other measures. The outcome measures with the lowest unexplained variance were Δ global health (43%) and Δ pain (41%) (Table 5-19).

Table 5-19: Regression of Δ fatigue and the Δ core set variables at 6- months

Measure (Δ 0-6 months) (n=45)	R multiple correlation	R2 % explained variance	1-R2 % unexplained variance	F (p) overall model significance
MAF	0.30	0.09 (09)	0.91 (91)	0.645 (.694)
CRP	0.21	0.06 (06)	0.94 (94)	0.404 (.872)
Swollen joint count	0.47	0.22 (22)	0.78 (78)	1.783 (.129)
Tender joint count	0.47	0.22 (22)	0.78 (78)	1.760 (.134)
HAQ	0.62	0.39 (39)	0.61 (61)	4.031 (.003)
Global Health	0.76	0.57 (57)	0.43 (43)	8.430 (<.001)
Pain	0.77	0.59 (59)	0.41 (41)	9.061 (<.001)

CRP, C-reactive protein. HAQ, health assessment questionnaire disability index; MAF, multidimensional assessment of fatigue-global fatigue index. R = multiple correlation coefficient with changes in the linear combination of the rest of the measures. R^2 = coefficient of determination or explained variance; proportion of variance in the measure associated. 1-R^2 = proportion of variance not predicted by the rest of the measures.

These results from both the 3 and 6-month data demonstrate that fatigue variance is largely unexplained by the core set outcome measures. Therefore, measuring the patient reported outcome fatigue, provides additional information on outcome in inflammatory arthritis that is unexplained by the conventional core set variables. This finding demonstrates the unique contribution made by fatigue to the comprehensive assessment of health outcome in inflammatory arthritis. Moreover, there was subtle difference between the magnitudes of the unexplained variance at each time of assessment, suggesting that the unexplained variance in fatigue differs over time with different states of disease activity.

To conclude, analyses to clarify the unique contribution of fatigue in the assessment of outcome in patients with inflammatory arthritis can be summarised as follows. The association demonstrated between MAF and the patient reported outcomes, pain, global health, and HAQ-disability index, was greater than with swollen and tender joint count and CRP, on univariate analysis at each time-point. While according to the multivariate model, which examined the complex interrelationships among the variables, the combination of variables most relevant to baseline fatigue were the HAQ disability index, global health, and C-reactive protein. Pain and tender joint count were most relevant to fatigue variance at 3-months, while at the 6-months time point the variance in fatigue levels was best explained by patient global health. These findings demonstrate that fatigue levels were influenced by different variables prior to and following initiation of TNFi therapy, probably due to disease status.

The variables most relevant to change in fatigue at 3-months were change in HAQ-disability index and global health. However, at 6-months post baseline the change in fatigue score was not influenced by the change scores in any of the core set variables. These interesting finding suggests that the variables which exert an influence on change in fatigue over time vary according to disease state. Fatigue outcome at 6-months following TNFi therapy was not fully explained by changes in the core set variables demonstrating that evaluation of fatigue provides unique information on patient outcome in inflammatory arthritis.

Measuring the patient reported outcome fatigue, the main variable of interest in this study, provides additional information on outcome in inflammatory arthritis above that provided by the conventional core set variables.

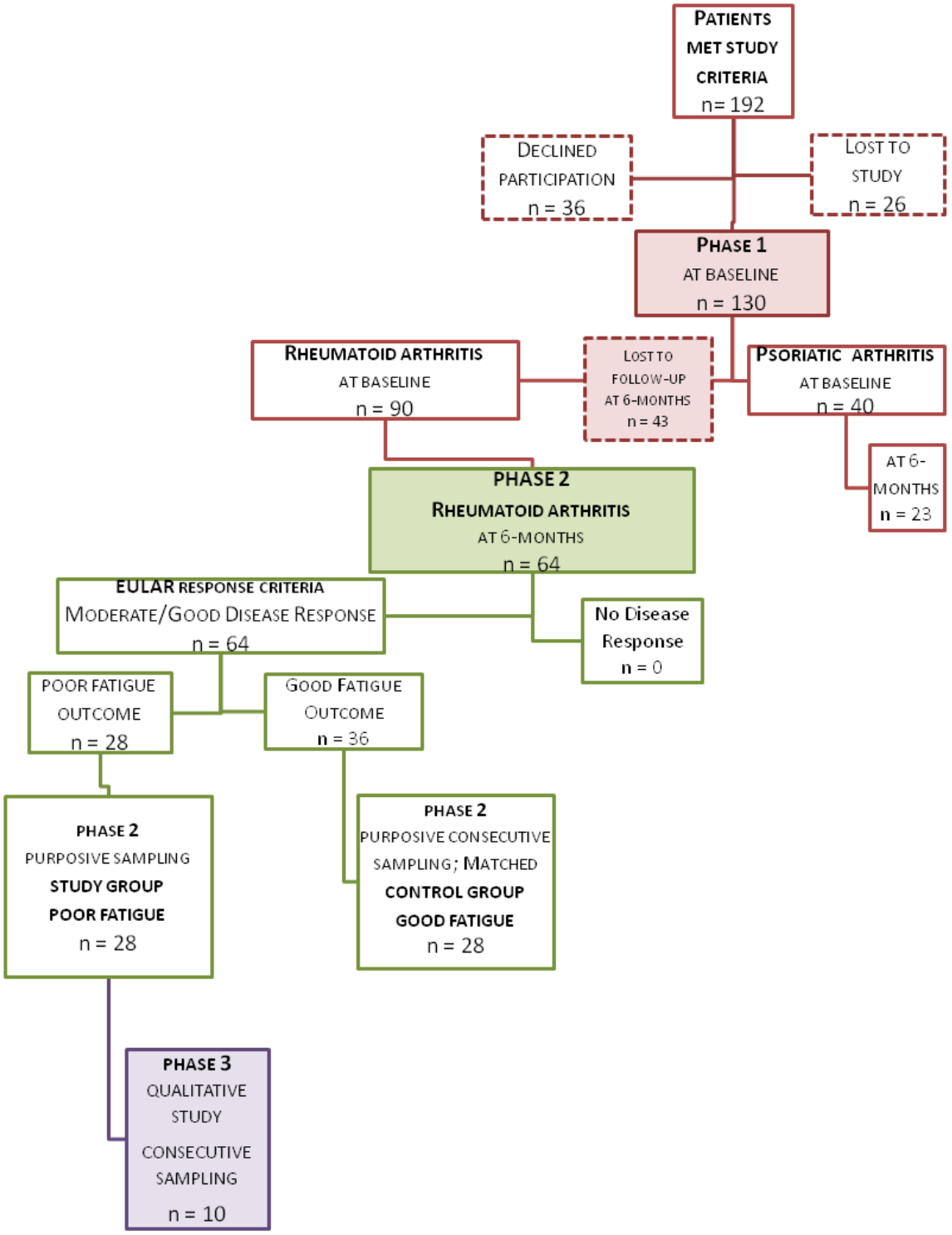
5.11 Clarification of the Unique Elements of Fatigue in the Assessment of Outcome in Patients with Rheumatoid Arthritis:

5.11.1 Comparative analysis of poor fatigue outcome and good fatigue outcome sub-groups

Having established the magnitude of the unique contribution made by fatigue to the assessment of outcome in patients with inflammatory arthritis the next stage of study focused on clarifying unexplained elements of the symptom of fatigue. A comparative, quantitative, prospective study of both a *Poor Fatigue Outcome* subgroup and a *Good Fatigue Outcome* subgroup was undertaken using questionnaires to capture information of possible contributory factors to persistent post treatment fatigue such as pain, self-efficacy, sleep, and mood.

A subgroup of patients with '*Poor Fatigue Outcome'* was identified at 6-month follow-up. These were patients with rheumatoid arthritis who continued to report moderate or greater fatigue on the verbal rating scale and at the same time demonstrated a moderate to good response in disease activity according to the EULAR Response Criteria (ERC) (Table 4-2). At the 6-month time point 28 (34%) patients who reported a moderate or greater fatigue despite demonstrating a moderate (ERC > 0.6), to good (ERC > 1.2) improvement in disease status were selected for further study (Figure 5-8). A control group (n=28) with '*Good Fatigue Outcome'* coupled with a good disease response was then selected to serve as a basis for comparison which reflected similar gender, age range, disease duration, and functional status as measured by the HAQ-disability index (Table 5-20).

Figure 5-8: Selection process and criteria for poor fatigue outcome subgroup



Subgroup data were tested for normality of distribution of the data using the Shapiro-Wilk test. A significance value of the Shapiro-Wilk Test greater the 0.05 denotes normally distributed data (Kinnear and Gray 2009) (Appendix 15). With the exception of HAQ-disability index and Haemoglobin levels all variables deviated from the normal distribution. Therefore the following combination of tests were used: inferential statistics included Chi-square test for nominal data, the parametric independent sample t-test for group means on the normally distributed scale variables, and the non-parametric Mann-Whitney-*U* test in data which deviated from the normal.

The *Good Fatigue Outcome* subgroup (control group) comprised patients with rheumatoid arthritis who demonstrated a moderate to good response in both disease activity and fatigue levels. Key clinical details of both groups are presented in Table 5-20. The majority of the patients were female. At the 6-month time point mean functional capacity according to the HAQ-disability index was 1.11 ± 0.6 (0-3) for the study group and 0.76 ± 0.5 (1-3) for the control group. This difference of 0.35 between the two groups exceeds the known clinical meaningful difference of 0.22 (Section 4.7). However, the difference was found to beyond statistical significance (t= 0.18; exact p= 0.07).

Table 5-20: Study characteristics of the poor fatigue outcome study group, and the good fatigue outcome control group

Patients Details n (study, control)		**Study Group n(%)**	**Control Group n(%)**
Female gender (n=28, 28)		22 (79)	23 (82)
Mean age ± SD (range), years (n=28,28),		58±11(26-77)	58 ±11 (23-81)
Mean disease duration ± SD (range), years (n=28, 28)		14 ±11 (0-36)	14 ±12 (0-39)
HAQ ± SD (n=27, 27)	Baseline	1.40 ± (0.58)	1.15 ± (0.59)
(n=26, 23)	3-months	0.99 ± (0.62)	0.88 ± (0.66)
(n=26, 16)	6-months	1.11 ± (0.62)	0.76 ± (0.55)

HAQ Health Assessment Questionnaire disability index

Table 5-21: Demographic and clinical details of poor fatigue outcome study group, and control group

Patients Characteristics n (study, control)		**Study Group n (valid %)**	**Control Group n (valid %)**
Smoking status: (n=27, 24)	Current	9 (32)	7 (29)
Educational background	Primary	7 (25)	4 (20)
(n=26, 21)	Secondary	12(43)	7 (35)
	Third Level	6 (21)	9 (45)
Rheumatoid factor:	Positive	15 (54)	4 (14)† p≤0.006
(n=28, 28)	Negative	13 (46)	23 (82)
Ever Failed DMARD	Yes	18 (64)	24 (86) † p<0.036
(n=28, 27)	No	10 (36)	3(11)
Ever Failed Biologic(n=30, 30)	No	0	0
Median Haemoglobin levels (range), g/dl:			
(n=17, 19)	Baseline	13 (7-15)	13 0 (7-16)
(n=12, 17)	3-months	14 (12-15)	13.7 (11-17)
(n=22, 13)	6-months	13 (9-15)	13.4 (9-17)
Early Morning Stiffness			
(n=28, 26)	Baseline	30 (0-1440)	37 (0-600)
(n=25, 26)	3-months	30 (0-1440)	4.5 (0-60)
(n= 27, 56)	6-months	10 (0-180)	10 (0-30)*p =0.001
Mean DAS-28 ± SD, (Min-Max)			
(n=28, 25)	Baseline	5.3± (0.9), (3.5-6.9)	4.9± (1.1),(3.1-7.3)
(n=27, 24)	3-months	3.4± (1.0), (1.9-6.5	2.9± (0.9),(1.4-4.5)
(n=28, 16)	6-months	3.3±(1.1), (1.7-5.8)	2.4± (0.7), (1.2-4.4)* p = 0.002

DMARD- disease modifying anti-rheumatic drugs. † Chi-square test for nominal data. * p=.001, Mann-Whitney U test of significance (2-tailed), for independent samples.

These significant differences identified between the study and the control group, in relation to rheumatoid factor status, and duration of early morning stiffness, along with the clinical meaningful difference in the HAQ-disability index, are all characteristics of poor disease outcome suggesting a causal model for persistent fatigue.

To further clarify possible contributory factors to fatigue questionnaires were administered to capture information on pain, self-efficacy, sleep, and mood. Pain was measured using the Short-Form McGill Pain Questionnaire, self-efficacy was measured using the Arthritis Self-Efficacy Scales, sleep was examined using the Pittsburg Sleep Quality Index and mood was assessed using 3 scales The Profile of Mood States, the Beck Depression Inventory and the Beck Helplessness Scale. All scales and their validity are described elsewhere (Section 4.8.2).

Diagnostic tests on results from all but one scale showed the data to deviate from the normal distribution therefore the non parametric test for independent groups (Mann-Whitney . was used to compare means between the two groups throughout (Appendix 15). The exception was the Arthritis Self-Efficacy Scales, where the pain variable was normally distributed so the test for the difference between two sample means used the parametric independent *t*-test. As the sample size was small the exact p value in preference to the asymptotic p value is reported.

5.12 Comparative Analysis of Pain between the Poor Fatigue Outcome and Good Fatigue Outcome Groups

The 3 main sections of the McGill Pain Questionnaire are summarised below: (Table 5-22). Section A which describes the pain, and section B rates the pain intensity, as experienced during the last week. Section C is concerned with rating current pain intensity (Appendix 16). There was a significant difference in pain experience between the groups in both the sensory subscale U = 0 251; exact p = 0.02 (Section A), and the overall scores of sections A, B, and C. For section A: Total Descriptor Score U = 0 241; exact p = 0.021. For section B: VAS for Pain Intensity U = 0 223; exact p = 0.023 and, for section C: Verbal Pain Intensity score U = 0 231; exact p = 0.009 (2-tailed).

Table 5-22: Short Form Mc Gill Pain Questionnaire (SF-MPQ): Comparative analysis of pain experience between study group and control group

	SF-MPQ-Descriptors (During Last Week) n (study, control) (range)	**Study Group**	**Control Group**	**p-value**
	Mean Sensory ± SD (range), (n=27,28) (0-33)	8.0 ± 6.4 (0-24)	5.2 ± 6.5 (0-23)	p= .02*
	Mean Affective ± SD (range), (n=27,28) (0-12)	2.7 ± 3.3 (0-12)	1.8 ± 2.8 (0-10)	p= .235
A:	**Total** Descriptor Score ± SD (range), (n=27,28) (0-45)	11.3 ± 9.4(0-33)	6.9 ± 8.9 (0-33)	p= .021*
B:	**Past Week**: VAS Pain Intensity Mean ±SD(range), (n=27,26) (0-100mm)	41.4±26.6(0-80)	24.4± 26.6(0-100)	p= .023*
C:	**Current**: Pain Intensity, n (valid %), (n=27, 28)			p= .009*
	No Pain	3 (11)	9 (32)	
	Mild	6 (22)	11 (39)	
	Discomforting	13 (48)	5 (18)	
	Distressing	3 (11)	2 (7)	
	Horrible	2 (7)	0	
	Excruciating	0	1 (3)	

See Methods Section 4.8.2. * Mann-Whitney U test of significance (2-tailed)

Evaluation of the individual components of the pain descriptors scale showed that the subgroups reported no significant difference in how they evaluated the 'affective' dimension of pain. However, significant differences between the sensory component of

pain descriptors, overall total descriptor score, pain intensity over the last week, and current pain intensity were consistent between groups. These finding suggest that the physiological pain experience dominated. Patients with poor fatigue outcome experienced more pain than patients with good fatigue outcome; this pain was mainly physiological rather than affective in nature.

5.13 Comparative Analysis of Arthritis Self-Efficacy between the Poor Fatigue Outcome and Good Fatigue Outcome Groups

Patient self-efficacy was measured using The Arthritis Self-Efficacy Scale (ASES) (Appendix 19) (Brady 2003). Results from the Arthritis Self Efficacy for Pain, Function, and Other Symptoms are presented (Table 5-23).

Table 5-23: Arthritis Self-Efficacy Sub-Scales: comparative analysis of arthritis self-efficacy between the poor fatigue outcome and good fatigue outcome groups

	Subscales	**Study Group**	**Control Group**	
	Self-Efficacy Pain: perceived ability to…	**Mean±SD**	**Mean±SD**	**p-value**
	n=28	**Scale Range 1-10**		
1	…decrease your pain quite a bit	5.9±2.0	6.1±3.0	=.418
2	…continue most of your daily activities	6.5±2.5	6.9±2.9	=.372
3	…keep arthritis pain from interfering with sleep	6.1±3.0	6.7±2.8	=.364
4	…make small/moderate reduction in pain…	5.5±2.7	4.5±2.9	=.185
5	…make large reduction in your arthritis pain	4.3±2.7	4.8±3.2	=.667
Mean Pain		**5.6±1.9**	**6.1±2.3**	**=.359**
Self-Efficacy Function: perceived ability to… n=28				
1	…Walk 100 feet on flat ground/ in 20 seconds	6.7±3.3	7.6±3.1	=.214
2	…Walk 10 steps downstairs in 7 seconds	6.3±3.3	6.7±3.1	=.556
3	…Get out of arm less chair quickly without using hands	5.7±3.4	6.7±3.1	=.236
4	…Un/button 3 buttons in a row in 12 seconds	6.8±3.1	7.7±2.4	=.226
5	Cut …meat with knife and fork in 8 seconds	6.8±3.2	7.5±2.7	=.425
6	…Turn an outdoor tap all the way on and…off	6.6±2.9	6.8±3.1	=.562
7	…Scratch your upper back/both right and left hands	5.1±3.3	5.8±3.3	=.414
8	Get in/out passenger side of car… unaided	7.2±25	7.7±2.9	=.605
9	…Put on long sleeve shirt/blouse… unaided/8sec.	7.2±2.9	8.2±2.5	=.107
Mean Function		**6.7±2.4**	**7.1±2.5**	**=.413**
Self-Efficacy Other Symptom: perceived ability to… n=28				
1	…Control your fatigue	4.9±2.4	6.1±2.3	=.068
2	…Regulate activity without aggravating joints	6.2±2.6	7.0±2.4	=.258
3	…do something to help...self feel better if feeing blue	6.1±2.7	7.4±2.7	=.044*
4	…Manage arthritis pain during daily activities	6.4±2.8	7.2±2.5	=.283
5	Mange arthritis symptoms...do… thing you enjoy doing	5.7±2.7	7.0±2.8	=.051
6	…Deal with frustration of arthritis	5.9±2.8	7.1±2.8	=.075
Mean Other Symptom		**5.8±2.4**	**7.2±2.2**	**=.022***

See Appendix 19 for exact wording on questionnaire

There was no difference between mean values for any of the individual self-efficacy for pain or the self-efficacy for functioning questions in either subscale. However, within the

self-efficacy for other symptoms subscale a statistically significant difference was seen between the mean values of the study group and control group for self-efficacy in relation to ability to do something to help themselves feel better when feeing blue; $U = 0.270$; exact p = 0.044 (2-tailed). No statistical difference was demonstrated between groups means for overall self-efficacy for pain $U = 0.335$; exact p = 0.359 (2-tailed), and self-efficacy for functioning subscales; $U = 0.341$; exact p = 0.413 (2-tailed). However, the difference between group means in self efficacy for other symptoms reached statistical significance: $U = 0.253$; exact p = 0.022 (2-tailed) (Table 5-24) indicating that the poor fatigue outcome group were less confident in their ability to managed arthritis related symptoms not related to pain and function.

Table 5-24: Arthritis Self-Efficacy Scale (ASES): Comparative analysis of self efficacy between study group and control group

Arthritis Self Efficacy Scale (scale range)	**Study Group n=28**	**Control Group n=28**	**P value**
Mean Pain Self-Efficacy ± SD (range), (1-10)	6 ± 1.9 (2-10)	6 ± 2.4 (2-10)	p=.359
Mean Functioning Self-Efficacy ± SD (range), (1-10)	7 ± 2.4 (2-10)	7 ± 2.5 (2-10)	p=.413
Mean Other Symptom Self-Efficacy ± SD, (range),(1-10)	6 ± 2.4 (1-10)	7 ± 2.2 (3-10)	p=.022*

See Methods Section 4:3:10. * Mann-Whitney *U* test of significance (2-tailed)

In summary, self-efficacy for both pain and functioning, or their subsets, were the same for both study and control group. However, patients in the study group had an overall lower self-efficacy in relation to other symptoms, the subset 'low self-belief in relation to managing low mood' being singularly significant.

5.14 Comparative Analysis of Sleep Quality between the Poor Fatigue Outcome and Good Fatigue Outcome Groups

Sleep was measured using the Pittsburgh Sleep Quality Index (Appendix 20); summary scores in both groups are presented (Table 5-25). No significant difference between groups was demonstrated for the overall PSQI. No significant difference was demonstrated between the groups for any of the subscales; the mean sleep duration approached significance for difference between the groups: $U = 0.284$; exact p = 0.061 (2-tailed). No difference was seen between the groups in the number of patients who used sleep medications. Twenty-one patients (75%) in the study group and 20 (71%) patients in the control group reported that during that previous four weeks they had not used any medicine to induce sleep.

Table 5-25: Pittsburgh Sleep Quality Index (PSQI): Comparative analysis of sleep quality between study group and control group

Pittsburgh Sleep Quality Index (range)	**Study Group n=28**	**Control Group n=28**	**p value**
Mean Sleep Duration ± SD (range) (0-3)	1.1 ± 1.1 (0-3)	0.6 ± 0.9 (0-3)	.061
Mean Sleep Disturbance ± SD (range) (0-3)	1.5 ± 1.0 (0-3)	1.5 ± 0.8 (0-3)	.901
Mean Sleep Latency ± SD (range) (0-3)	1.4 ± 1.1 (0-3)	1.3 ± 1.0 (0-3)	.856
Mean Daytime Dysfunction ±SD (range)(0-3)	1.2 ± 1.0 (0-3)	1.0 ± 0.8 (0-3)	.805
Mean Sleep Efficiency ± SD (range) (0-3)	1.4 ± 1.2 (0-3)	1.2 ± 1.1 (0-3)	.808
Mean Overall Sleep Quality ± SD(range)(0-3)	1.2 ± 1.2 (0-3)	1.0 ± 0.9 (0-3)	.832
Mean Sleep Medications ± SD (range)(0-3)	0.7 ± 1.2 (0-3)	0.5 ± 0.9 (0-3)	.966
Mean Total PSQI ± SD (range) (0-21)	**8.3 ± 3.6 (4-16)**	**7.3 ± 4.5 (0-18)**	**.319**

See Methods Section 4.6.2. * Mann-Whitney *U* test of significance (2-tailed)

Patients from both the study group and the control group reported similarly high global PSQI scores (8 and 7 respectively), which were not statistically different. However, a score greater than 5 is clinically indicative of poor sleep quality. In summary, patients with both poor fatigue outcome and good fatigue outcome experienced poor sleep quality according to the global PSQI.

5.15 Comparative Analysis of Mood between the Poor Fatigue Outcome and Good Fatigue Outcome Groups

Mood was evaluated using the Profile of Moods States (POMS), the Beck Depression Inventory (BDI) and the Beck Hopelessness Scale (BHS) (Appendices 21-23). The 3 separate mood scales used in this comparative study are presented (Table 5-26).

No statistical difference was found between the study group and the control group on either mean values on the subscales, or mean total scores on the Profile of Mood States.

Table 5-26: Profile of Mood States; Beck Depression Inventory, Beck Hopelessness Scale: Comparative analysis between study group and control group

Profile of Mood States n (study, control) (Scale range)	**Study Group** Mean (SD), range	**Control Group** Mean (SD), range	**p value**
Depression-Dejection (n=28,28) (0-32)	4.8 ± 5.4 (0-19)	3.3 ±5.2 (0-20)	.102
Vigor-Activity (n=28,28) (0-24)	7.0 ± 5.6 (0-18)	8.5 ± 5.7 (0-20)	.293
Anger-Hostility, (n=28,28) (0-28)	3.9 ± 4.5 (0-18)	2.4 ± 2.9 (0-9)	.134
Tension-Anxiety (n=28,28) (0-24)	4.1 ± 3.8 (0-13)	3.6 ± 4.3 (0-16)	.351
Confusion-Bewilderment (n=28,28) (0-20)	2.1 ± 1.9 (0-8)	2.1 ± 3.0 (0-10)	.324
Fatigue-Inertia (n=28,28) (0-20)	5.7 ± 4.9 (0-20)	5.6 ± 5.8 (0-21)	.469
POMS Total (n=28,28) (0-100)	13.7 ± 19.8 (14-59)	8.6±18.4 (18-49)	.306
Beck Depression Inventory (BDI)			
Level of Depression * (n=28,28) (0-100)	11.8± 7.5 (1-35)	8.2 ± 6.6 (0-26)	.037*
Beck Hopelessness Scale (BHS)			
Level of Hopelessness (negative attitude) (n=28,28) (0-100)	5.9 ± 5.0 (0-19)	4.2 ± 4.0 (0-16)	.111

See Methods Section 4.8.2

The mean Beck Hopelessness Scale ± SD (range) for the study group of 5.9 ± 5.0 (0-19), did not differ significantly from that of the control group 4.2 ± 4.0 (0-16). However, the mean Beck Depression Score ± SD (range), of 11.8 ± 7.5 (1-35) for the study group was

shown to be statistically different from that of the control group 8.2 ± 6.6 (0-26); U = 265; exact p = 0.037 (2-tailed). Total scores on the Beck Depression Inventory were in what is considered to be the mild (0-13) to moderate range (14-19) for depression. When the one outlier on the scale (BDI score 35) was removed from the data set of the poor fatigue outcome group the statistical difference between both groups was beyond statistical significance U = 0 265; exact p = 0.058 (2-tailed).

No significant difference was seen in mood levels between groups.

5.16 Conclusion

This comparative component of study of the *Poor Fatigue Outcome* subgroup and the *Good Fatigue Outcome* subgroup established that patients with poor fatigue outcome experienced more pain. They reported less belief in their own ability to self-manage their various symptoms of arthritis, including their fatigue, more than symptoms related to pain and functioning.

5.17 Qualitative Study of the Phenomenon of Fatigue through Content Analyses

This supplemental qualitative phase of study provided further enlightenment on the unique elements of persistent fatigue, from the perspective of those who experience this symptom, in order to contribute to the further explanation and refinement of the results from the quantitative phase of study. Data analysis used the techniques of qualitative content analysis, following a three step process of data reduction, data display and abstraction of conclusions (Miles and Huberman 1994). This analytic process included, a) coding of data from transcribed text and recordings, b) recording of the researcher's own insights and reflections on the data and the context, c) data sorting to identify similar phrases, patterns, categories, important features within the participants responses, and themes, d) identifying commonalities and differences between the data sets and extracting these for further deliberation and consideration, e) suggestion of low level generalisations which could be substantiated by the data and f) examining such generalisations in the context of existing knowledge from previous research and from the quantitative phase of study.

5.17.1 Characteristics of participants

A summary of fatigue levels, disability index, disease activity and improvement scores at 6-months, in the patients interviewed, is presented (Table 5-27). Interviews were conducted with the assistance of ten patients, six of whom were female. Age range was 44-75 years, and the disease duration ranged between 6 and 36 years. Six participants were rheumatoid factor positive. Two of the participants were current smokers. Multidimensional assessment of fatigue scores ranged from 20.4 to 42.7 (scale range 1-50), representing moderate to severe fatigue levels. Functional impairment according to the HAQ-disability index (HAQ) ranged between mild/moderate (HAQ≥1) and moderate/severe (HAQ≥2.25). In accordance with the EULAR Response Criteria all ten patients interviewed had demonstrated a moderate (>0.6) to good response (>1.2) in their disease activity score from baseline, at the 6-month time point.

Table 5-27: Patient clinical characteristics

No.	Gender M, male, F, female (age),years	Disease Duration Years	MAF	HAQ	DAS28 at Baseline	DAS28 at 6-months	DAS28 Improvement from Baseline (EULAR Response Criteria)
IV1	F (48)	25	38.9	1.875	5.64	4.8	0.8 (1)
IV2*	F (75)	6	33.5	1.375	5.23	2.3	2.9 (2)
IV3	M (62)	30	24.5	1.0	4.20	3.3	0.9 (1)
IV4	F (50)†	6	34.0	1.0	4.20	3.4	0.8 (1)
IV5*	M (60)	36	20.5	1.25	4.39	1.9	2.5 (2)
IV6*	M (60)	20	24.0	1.25	5.09	2.8	2.3 (2)
IV7*	F (44)	6	28.8	1.5	6.86	5.0	1.9 (2)
IV8*	F (65)†	26	42.7	2.25	6.39	4.7	1.7 (2)
IV9*	M (69)	35	20.4	1.375	5.13	2.5	2.6 (2)
IV10	F (57)	16	30.3	1.0	6.90	2.9	4.0 (2)

IV, interviewee. * Rheumatoid Factor Positive. † Current smoker. MAF, Multidimensional Assessment of Fatigue Scale. HAQ, Health Assessment Questionnaire-Disability Index. DAS28, Disease Activity Score 28. Eular Response Criteria: 0 None, 1 Moderate, 2 Good Improvement in DAS28 from Baseline.

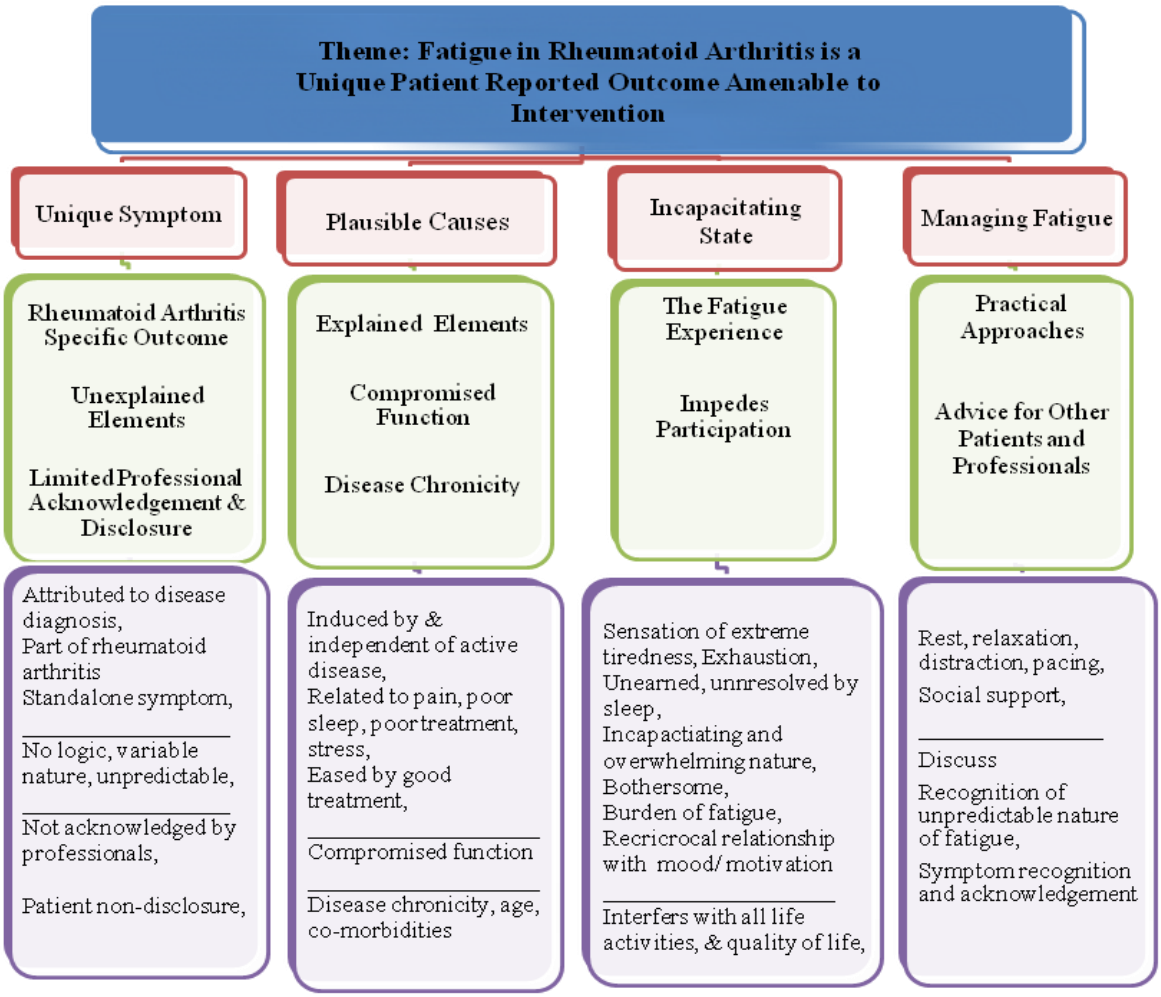
Three participants had completed primary level education, six had completed second level and one participant had completed third level education. Past failure of disease modifying anti-rheumatic medication was reported in seven cases, and no participant reported failure to respond to a previous biologic therapy. Haemoglobin levels were essentially normal with median (range) g/dl values of 14 (11-15). At the 6-month time point participants reported median early morning stiffness (range), minutes of 30 (2-60).

5.17.2 Qualitative findings

One overarching theme emerged from the analysis of the narrative data supported by four main categories, and ten subcategories in relation to patients' perception of fatigue. The overarching theme was: Fatigue, in rheumatoid arthritis, is a unique patient reported outcome amenable to measurement and intervention (Figure 5-9). The four categories were: -

I. Unique symptom of rheumatoid arthritis
II. Plausible causes of fatigue
III. Incapacitating and irresolvable state
IV. Managing fatigue

Figure 5-9: Model of the fatigue experience in rheumatoid arthritis: overarching theme; categories; subcategories; codes



5.17.3 Category I: Unique symptom of rheumatoid arthritis

Patients' symptom experience was explored in relation to their perception of fatigue, and their evaluation or judgement of the meaning of this symptom. The data were explored for distinguishing quality attributes guided by the research objective to identify unexplained elements of fatigue in the assessment of outcome in rheumatoid arthritis and identify potential modifiable factors to improve fatigue outcome.

Subcategory: A specific outcome in rheumatoid arthritis

The narrative data supported the contention that for some patients fatigue means something quite distinct from other symptoms associated with rheumatoid arthritis. Fatigue was perceived as another individual component of arthritis and evaluated as a symptom whose onset coincided with, and was therefore attributed to the diagnosis of rheumatoid arthritis, by most patients. One female with relatively short disease duration of six years was adamant that fatigue was not a feature in her life prior to developing rheumatoid arthritis:

> IV7:3 "New to me...since arthritis started".

This was also reflected by a gentleman with disease duration of twenty years, who with clarity of recall claimed never experiencing fatigue prior to receiving his diagnosis:

> IV6:10 "Before I got arthritis I did not suffer with this".

This particular patient regarded fatigue as a standalone symptom. He continued to experience fatigue even though, he evaluated his arthritis as being under control, and his pain levels as minimal to none. He also denied having any significant stress in his life:

> IV6:24 "But it's not the arthritis [disease activity or flare] or pain, it's just I feel exhausted".

Another female patient had long disease duration of 26 years, and obvious major joint destruction and deformity, and a similarly long standing diagnosis of depression. However, she distinguished the experience of 'tiredness' associated with arthritis from the tiredness which she had experienced over the years, associated with her periodic bouts of depression. Perhaps her belief was intuitive more than logical; nonetheless, she was clear that her rheumatoid arthritis was the cause of 'the fatigue' being explored during interview:

> IV8:12 "…I don't know why I think it but that's what I felt" [that tiredness came from the arthritis].

Fatigue was experienced as a standalone symptom in the sense that patients perceived their 'tiredness' to be a specific outcome of their rheumatoid arthritis:

While it is argued that all dimensions of fatigue are a consequence of the more classic documented symptoms of inflammatory arthritis, such as painful inflamed joints, and functional impairment (Pollard *et al.* 2006), the perspective of those with the lived experience was not one of ready agreement. Having experienced multiple symptoms at one time or another, associated with her rheumatoid arthritis, one lady had disentangled the overlapping effect of multiple symptoms. She had isolated fatigue as an independent symptom of her rheumatoid arthritis independent of pain and functional limitation:

> IV4:4 "I kind of became more conscious of it [when not in pain] because when you were sore you were kind of limited to what you were doing anyway, and like that some days I would get up and I would say I would love to wash the windows but I haven't got the energy to do it…you know never mind whether I am capable [have physical dexterity] of doing it or I am not, I know I haven't got the energy to do it".

While some patients recognised fatigue as being independent of disease duration and pain for most fatigue was regarded as the unofficial 'classic' symptom of rheumatoid arthritis:

> IV6:7 "its par for the course".
>
> IV2:27 "…with arthritis you will always have some fatigue…its part of it"

The attribution of the source of fatigue to rheumatoid arthritis was manifestly expressed by some, while in almost all interviews the sentiment was inferred as opposed to being explicitly stated.

Subcategory: Unexplained Elements

There were many unexplained elements to fatigue. Patterns related to timing of fatigue onset, voiced by patients, were variable and lacked logic, because fatigue could "kick off any time" (IV6:12). Onset might coincide with waking, or occur two hours after getting up or during the day, it may also be a gradual onset over hours or days, or occur in a spasmodic way:

> IV 4:9 "Some days I am tired before I even get out of bed"
>
> IV4:19 "I don't understand it…it varies, it comes and goes some days other days it is there from the time you get up".
>
> IV7:24 "it comes on gradually…just over a day ya maybe less…it would last for a few days or a week"

For a few, fatigue was more noticeable in the absence of symptoms of active disease and as such was not linked to disease activity status:

> IV4:4 "I think I noticed it when I started feeling better …when the aches and pains start subsiding"

However, most patients found it difficult and therefore they found it difficult to explain:

> IV4:7 "I just don't understand it myself, it doesn't make sense"
>
> IV6:4 "I just don't know"…"again, it can just happen".

Patients largely explained the symptom of fatigue by attributing it to their diagnosis of rheumatoid arthritis as opposed to regarding it as a consequence of the other symptoms of the disease, such as pain, poor sleep:

> IV7:20 “I think it’s different because it’s not the sort of tiredness because of lack of sleep, and I have no energy…no sometimes it’s just …it’s there”.
>
> IV9:17 “there is no logic…it just goes its course itself…”

Subcategory: Limited Professional Acknowledgement and Patient Disclosure

Lack of recognition of fatigue as a unique symptom negatively affected symptom management at a professional level. Receiving or seeking professional advice from doctors or members of the health care team was not a usual occurrence for this group of patients. Most patients categorically denied ever being asked about or advised about fatigue; instead they experienced being asked about other symptoms such as functional ability:

> IV4:30 “No … No I don’t think so [ever asked about fatigue] I don’t really…, no…I would have been asked how I get around things I cannot do”.

Where the experience of having being asked about the presence or absence of fatigue was reported no further discussion around the topic, or any further follow-up, had taken place. In this patients experience fatigue was given only a cursory mention:

> IV3:35 “I just think it’s like them saying how is the weather?…and leaving it like that”.

The experience of most patients was that clinical assessments, advice, and support received from doctors and the health care team primarily focused on the symptoms of pain and functional ability; the conventionally recognised symptoms of the core set of outcome measures for rheumatoid arthritis (Felson *et al.* 1993). Patients were not accustomed to being questioned directly about their fatigue; the experience was that doctors prioritised pain management:

> IV6:30 “main focus is to control the pain…doctors want to control the pain”.

Nor did patients themselves frequently acknowledge fatigue symptoms in the clinical setting:

> IV8:12 "I feel that I would be complaining of something [fatigue] that I shouldn't you know".

Instead they both excused and were tolerant of the fact that this major symptom was largely ignored. In their own way, they subconsciously contributed to the inactivity and avoidance in relation to the challenge of fatigue:

> IV8:27 "they will ask me how I am…it [fatigue] is probably what they mean of course".

Doctors and the health care team were excused from attempting to help manage this challenging symptom on the basis that nothing can be prescribed for fatigue; therefore, patients perceived that they had to endure, accept and manage this symptom largely unassisted:

> IV7:26 "there isn't much they can do about that, they give tablets for pain but you know you can't with fatigue it's something that you have got to do"[self-manage your symptom of fatigue].

The majority of the interviewees mentioned that outside of their medical consultation they seldom discussed their diagnosis of rheumatoid arthritis, other than briefly with their partner or family. This was based on a belief that firstly, people would not want to know, and that secondly, it was important that a person's sense of identity was not lost to the chronic medical condition. Moreover, in relation to the symptom of fatigue, patients engaged in a form of non-disclosure. There was reluctance if not indeed a conspiracy of silence when it came to discussing fatigue either with significant others. More especially patients were reluctant to talk about their fatigue to the doctor not wishing to complain, and believing that they should cope better:

> IV2:7 “No I find it hard to complain [about fatigue] because I feel I should be able to cope”

Patients therefore seem to believe that they carry the responsibility for the management of this symptom without receiving any professional or formal advice, instruction or supportive intervention on how to do so. One man who appeared well adjusted to his long established disease said the main reason he disclosed and sought help for fatigue was when its intensity and duration reached an incapacitating and relentless state:

> IV9:2 “depends how long it lasts before I would decide what I will say…no energy, no strength, can’t do nothing…can you do something to help me?”

Perhaps this could be explained by the belief that little could be done for fatigue or that pain and function were more of a priority, especially on first presentation, and by default remained the focus of ongoing management priorities. Such insight provides a basis for options for interventions in the management of this patient reported symptom.

5.17.4 Category II: Plausible causes of fatigue

Subcategory: Explained Elements

The numerous potential contributory factors to fatigue voiced consisted of a combination of disease status, and disease related factors. These included an active disease state, pain, disturbed sleep pattern, strain from use of sore joints, increased effort required in using damaged joints and soft tissues, and lack of appropriate treatment for the disease. Most patients associated the presence of fatigue with the presence of pain, both acute and chronic pain:

> IV1:6 “I don’t mind the joints swelling if I am not in constant pain, but whenever I am in constant pain I think that’s what makes me feel tired” .

IV4:4 “I noticed it when I was in a lot of pain”…

Fatigue was also seen as a feature of active disease by most:

IV1:6 “I wouldn’t have been as tired when the treatment was working like when the arthritis wasn’t …as active”.

IV1:3 “Well if it hasn’t been too active [the arthritis]…I wouldn’t feel as tired…”

IV4:11 “Yes because when I was in a bad way with the arthritis, I was really really tired all the time”

The long term consequence of a disturbed sleep pattern on account of joint pain and discomfort was mooted as a cause of fatigue by only one patient interviewed:

IV6:11 “because of the joint problems and sometimes I would stay up all night with the pain… But then again I would sleep all day you know… Or sleep half the night my sleeping pattern was mixed up, and from that I had got some fatigue. But the latter years seemed to have got worst”

IV7:5 “it could be …I don’t sleep properly sometimes…a lot of tossing and turning…with the joints…if I have been laying awkwardly then the pain will wake me up”

The majority of patients believed that pain and disease activity were the two major causes of fatigue and that fatigue was more pronounced during a disease flare. For most Patients modern biologic therapies were seen as a treatment that positively influenced this symptom.

IV3:35 “when I get [TNFi therapy]…it is like I am being energised”.

IV10:13 “Well before I got the [TNFi therapy] I sat on a chair all day, the fatigue was so bad…you know it [TNFi therapy] has given me back good quality you know even though I might be tired [normal/explained tiredness] but I expect that”.

The varied perceptions included fatigue as being an integral part of rheumatoid arthritis, exacerbated by pain, mostly absent when medication was working. However, occasionally fatigue was more noticeable the day of, and after taking medication, such as weekly methotrexate or periodic biologic therapy. Fatigue was reported as being independent of sleep quality, and absent when disease not flared. These multiple potential contributory factors stood as testimony to the enigmatic nature of the symptom as alluded to by most patients. Perhaps the incongruity between the explained and unexplained nature of fatigue is due in part to the well recognised and documented unpredictable disease course that is rheumatoid arthritis.

Subcategory: Compromised Function

The extra effort required for all activity on account of compromised joint function was also suggested as a cause of fatigue. Fatigue was therefore regarded as being a consequence of physical disability..."probably because it takes longer to do things" IV2:11. Compromised physical dexterity and functional disability was also acknowledged as a factor that contributed to an increased level of frustration and negative mood, adding to the fatigue experience:

> IV4:11 "well everything is much slower [upper and lower limb function] you know, and by the time you are half way through you get fed up anyway".

While these plausible explanations for fatigue were proposed, nonetheless, fatigue was more generally regarded and accepted as an unexplained part of the disease entity of rheumatoid arthritis.

One man referred to the increased effort required due to compromised dexterity and constant demand for self-management of all the various aspects of arthritis. This placed a constant drain on patients' physical and emotional reserve; in this way the pervasive nature of this chronic and disabling disease contributed to the fatigue experience.

> IV5:9 "Just I suppose [fatigue is] heaviness of the body really. I suppose when it's out its very out [energy]; Just not able to make that first move. No it's kind of heaviness and you don't really want to do something. You would be slower starting…just not able to make that first move, get going and get up off the chair".

Subcategory: Ageing, and Co-Morbidities

Some patients suggested their other health conditions as possible contributors to fatigue, such as asthma, anaemia, bronchiectasis, and hypertension. A gentleman with mild asthma wondered if it caused his fatigue:

> IV6:12 "…I often thought that cause I am not getting enough air in …that I am getting starved of oxygen which would lower my level of [energy]".

Ageing was tentatively proposed as a possible cause by a female septuagenarian, who frequently went for a seven mile walk along the beach. However, when asked if convinced that ageing was a contributory factor to fatigue she answered with conviction "no, no I'm not" (IV2:14). Like most of the other interviewees there was an overall tendency to identify the fatigue associated with arthritis as being part of their condition of rheumatoid arthritis.

5.17.5 Category III: Incapacitating state

Subcategory: The Fatigue Experience

A broad array of verbal indicators was used by patients to express the meaning of the experience of fatigue. These reflected many dimensions such as symptom quality, severity, and pattern of onset, domination, duration of fatigue, and inexplicable nature. The word

used by most all ten patients in this study to verbalise what fatigue meant to them was ‘tiredness’.

> IV1:1…“To me it just means tiredness, I get kind of waves of tiredness”
>
> IV6:3 “I take it as being tiredness, extreme tiredness.

Other descriptors used included ‘no energy’, ‘dwindling energy’, ‘no get up and go’, ‘lagged out’, ‘no strength’, feeling ‘a lot more tired than normal’, ‘heaviness of the body really’, ‘it’s hardness in your body’, ‘flat battery’:

Patients described what this fatigue felt like for them by giving insight into the qualities of this symptom through the ways that it manifests itself. Fatigue related to their rheumatoid arthritis was seen as ‘extreme tiredness’; it was experienced as irresolvable in the sense that it did not respond to rest and sleep when compared with normal tiredness. It was seen as a non-negotiable form of tiredness in the sense of it being an impossible symptom to ignore, or work through:

> IV2:4 “You just get this dreadful tiredness…and you can’t pull yourself out of it you know”.
>
> IV9:11 “Sometimes I would fall asleep…and I could still feel as bad when I woke up you know”

A distinction was drawn between ‘normal tiredness’, and tiredness of another type. One female interviewee of 75 years who was a lifelong master of yoga clearly distinguished fatigue from tiredness. With regular tiredness as she described it, it was possible to force yourself to carry on with whatever you were doing. However, arthritis related fatigue or ‘dreadful tiredness’ was experienced as incapacitating, associated with no reserve of energy to carry on with:

> IV2:4 “You just get this dreadful tiredness …I wouldn’t associate fatigue with tiredness,-normally - I can force myself”.

The other descriptive terms used such as ‘heaviness in the body’, ‘no energy’, ‘flat battery’, ‘lagged out’; are terms not in keeping with the normal human state of temporary loss of strength or energy. One 60 years old male who had lived with rheumatoid arthritis for thirty five years, maintaining full employment in spite of severe disease, and who had experienced times both with and without fatigue, stressed that there was a clear difference between what was normal and what was unusual tiredness:

> IV6:23 “Tiredness and fatigue…different things. I can get tired [normal tired] and I might sit down and have a cup of tea and I will get up and go again [after a rest]. [with] fatigue…I just don’t …”

This highlights the challenge of trying to deal with and manage this symptom experience.

Patients’ evaluations of fatigue intensity, distress and timing also ranged along a continuum of mild to severe for each of these dimensions. Most patients experienced a mild level of fatigue of variable duration and periodicity. However, even when regarded as being of a mild form overall, the notion of enduring constant fatigue was perceived as an intolerable burden. The following statement from one lady when asked if she experienced fatigue on a daily basis highlights the difficult nature of the fatigue experience:

> IV2:4 “oh no not every day, I would be dead if I did you know”.

The experience of some was that even in the absence of the major symptoms of painful, swollen, and inflamed joints, fatigue still negatively affected quality of life. One male reported how he was still bothered by the persistent nature of fatigue even when he regarded his lifestyle as being stable, and evaluated his disease status and pain control as good:

> IV6:7 “I would be doing the same thing at work [uneventful] … when I am relaxing; I wouldn’t be stressing myself out… I don’t suffer with little or no pain …It’s under control now [arthritis and pain], I would say very well under control over that last few years…[however] the fatigue is still there”

Along with fatigue, low mood or depressive episodes, in varying degrees, were parts of the symptom repertoire ever experienced by patients. However, there was reluctance among patients to support the idea that fatigue was an absolute consequence of low mood or depressive symptoms. More usually, it was believed that low mood was generally a sequel of this 'tiredness'.

> IV7:13 "I think it [low mood] comes after [fatigue]"
>
> IV10:8 "I would be in bad humour" [when fatigued]

While the reciprocal relationship between fatigue and motivation or mood had been experienced by patients, the intertwined nature of both states was difficult for patients to unravel:

> IV6:29 "Unless it is depression but I don't think I suffer from depression. I couldn't explain depression to you because I don't think I ever had it".

In this way patients distinguished between fatigue a symptom of depression and fatigue a symptom of rheumatoid arthritis.

Subcategory: Impedes Participation

Reflecting on the fatigue experience invariably led to patients describing the consequences of this symptom experience. One of the major consequences of fatigue experienced by those interviewed was that it interfered with participation in life. This interference spanned occupational, domestic, social and leisure activities.

> IV1:1 "I feel sometimes that I have to sit down and I am not able to go any further… you know".

Its impact on occupations was expressed by those in paid employment. The experience was that whenever or wherever fatigue occurred it had at the very least hindered if not impeded participation:

> IV6:6 "I could drive from my home in the morning to work, stop the car and fall asleep in the car".

When fatigue was experienced in the workplace it was necessary to reduce performance levels. There was also the associated burden of feeling that performance was compromised and suboptimal.

> IV7:5/29 "I just kind of take it as easy as I can…when I am tired I tend to make more mistakes"

The above quote was by a lady employed in the retail sector who worked between the check out desk and the cash office. She maintained that it was the symptom of tiredness as opposed to the symptom of pain which would cause her to make mistakes at her work.

Fatigue was reported to interfere with home, domestic, and personal activities. The negative effect of fatigue on performance sometimes spilled into home life as free time from work could be spent on fatigue enforced rest. Similarly, interference with domestic activities was attributed to fatigue by those in non-paid work also.

> IV4:24 "Yes it has changed where we say I use to be able to clean the house from top to bottom within an hour or 2 hours right. Now it could take me a week".

Lack of energy was another term used when referring to fatigue and its impact: IV7:3 "when I get home from work I have no energy at all…sometimes I have even gone to bed for a rest". This lack of energy combined with arthritis related functional limitations, and

coupled with the desire to maintain normality with one's peers conspired to hamper social participation.

> IV1:24 "I am not able to do as much as what I was…even go for a walk like, go places …because I don't feel that I ever have the energy …I don't want to be…slowing other people".
>
> IV6:6 "I can just get this fatigue ya that I am not able to… I wouldn't be in the humour to watch television, I might be watching a programme and if …my wife asks me what it is about I wouldn't be able to tell her".

This patient experienced fatigue as a disability and was reluctant to highlight feeling disabled due to the symptom of 'fatigue', to her family and friends.

Fatigue not only interfered with perception of competence and participation in work, it also affected concentration levels when relaxing and motivation for activities of daily living such as attending to personal hygiene.

> IV4:25 "sometimes I can't think straight, you know if you are trying to add things up".
>
> IV9:19 "With the fatigue I felt I would look at myself and say ah I am not going to shave today I don't have to shave, you know".

This overwhelming nature of fatigue was a common thread running through all interviews.

5.17.6 Category IV: Managing fatigue

The exploration of strategies availed of by patients in the management of the symptom of fatigue fell into two subcategories. One subcategory dealt with how patients themselves approached management of fatigue, another highlighted how patients might advise others, on the basis of their lived experience, on dealing with this symptom of inflammatory arthritis. The experience that fatigue remained an under discussed symptom meant that

management strategies were self devised and self-learned for the most part, and that patients were not inclined to talk about fatigue during clinical consultations.

Subcategory: Practical Approaches

All patients used a combination of rest, relaxation, distraction techniques, and pacing of activities and lifestyle as methods of coping with fatigue. Distraction techniques resorted to were a mixture of both active and passive behaviours. Active behaviours included taking time out to sit and read:

> IV2:19 "Well I try if I can stop you know to stop it, I just want to go up to the room and read you know"

Passive behaviours included sitting, internet browsing, or going to bed to either rest or sleep:

> IV9:22 "There was times I did go up and lie down in the bed"
>
> IV5:22"turn on the internet or something nothing that takes too much physical energy".

The company of friends was regarded as a helpful distraction when experiencing fatigue:

> IV9:20 "I would notice when they were gone [visiting friend] I am feeling a bit better you know".

Another expressed coping mechanism was acknowledgement of the presence of fatigue to oneself or to either a friend/partner so that an allowance is made, and that the patients' needs are accommodated.

IV2:22 “acknowledging it and pacing yourself”

IV6:26 “it helps for her [wife] to understand she doesn’t expect any more from me, she will allow for that”.

Self-management strategies were influenced by different attitudes and reactions towards the presence of fatigue which prevailed. Overall patients seem to adopt a pragmatic approach:

IV5:16/17 “I fight it [fatigue] you know…I just ignore it”.

IV2:19 “Well I try if I can …you know to stop it [fatigue]; I just want to go up to the room and read you know. Take time out”.

More active behaviours included pacing and planning. All patients used forms of pacing as part of their lifestyle to help prevent, and deal with the presence of fatigue; this was seen as a necessary learned behaviour. In that same way more forward planning was required for participation in evening social activities, that is, a period of rest was necessary before an evening out. This was regarded as a way of working around fatigue:

IV4:31 “…if I thought I was going to be tired that night I would go to bed for an hour so I am not tired”.

IV4:32 “pace yourself, pace yourself…you learn to pace yourself basically”.

One patient had transferred his pain management skills to the management of his fatigue. This gentleman with long standing disease of more than 30 years had recently participated in a formal self-management course on ‘Living Well with Arthritis’. He spoke of the merits of his newly learned self-management strategies, particularly pacing. Not only did he find he was more productive, when painting and decorating in his home, when he paced himself, he also avoided becoming fatigued:

IV 9:12 “And when I did that [time management while wallpapering] I stopped I went into the kitchen and I had a drink of something or other and sat down [for rest, then], back in and I did the other one the same way”.

IV9:11 “I got through an awful lot more work without fatigue”.

Subcategory: Advice for Other Patients

When asked how they would advise other patients and more especially what advice health carers could and should give others, patients drew from the experience of using combinations of the aforementioned strategies. And for the health professionals they had pearls of wisdom, grounded in their lived experiences, to offer. Most emphasised the need for pacing to minimise as opposed to prevent fatigue. A sense prevailed that prevention of fatigue was not possible as fatigue was seen as being “*par for the course*” (IV6:20). Advice offered for sharing with other patients included:

IV7:29 “important not to overdo it”.

IV6:20; “and that there was no one known and effective way of managing it”.

IV9:17 “there is no magic at home or in the pharmacy”.

While the above quote appears somewhat negative, however, there was a sense that recognition and acknowledgment of the realness of fatigue as a unique symptom of rheumatoid arthritis was important and promoted as a positive way of supporting patients in finding ways to deal with this symptom. For this reason it was suggested that as part of a pro-active management strategy all patients should be advised that fatigue is a symptom of rheumatoid arthritis:

IV1:23 “…I suppose talk about it… and maybe tell them more of what the symptoms are really like, the tiredness and that”.

IV9:27 “…say you are like that at times”.

These quotes represents the belief expressed that endorsement and validation of fatigue as a real symptom is something that health educators and health professionals should do

proactively in order to help patients cope. Perhaps this advice stemmed from their experience of fatigue as the under recognised symptom.

5.18 Conclusion

This supplemental qualitative study provided further enlightenment on unique elements of fatigue along with an explanation and refinement of the results from the longitudinal study. Patients identified with the symptom of fatigue as an integral part of the disease entity of rheumatoid arthritis. While on the one hand they proposed many rational and plausible disease and non disease related causes of their fatigue on the other they also had experienced a type of fatigue that could only be explained as being an integral part of their chronic rheumatic condition. They had devised methods of accommodating the symptom and its consequences in the absence of professional recognition or advice on management.

Chapter 6 Discussion

6.1 Introduction

The phenomenon of fatigue in patients with inflammatory arthritis prescribed TNFi therapy was the subject of this mixed methods study. The purpose was to determine the clinical characteristics of, contributory factors to, and some of the unexplained elements of fatigue in patients with rheumatoid arthritis and psoriatic arthritis from both the clinical and patients' perspectives. It was designed to inform practice by providing information on measurement as well as on a basis for effective interventions and management strategies. Mixing methods provided answers, grounded in both the objective and subjective perspectives, through five separate study objectives which explained and explored the phenomenon of fatigue. The first four objectives were addressed in the dominant quantitative phase of study. Levels of fatigue were quantified in patients with rheumatoid arthritis and psoriatic arthritis, and the measurement properties of a one-dimensional verbal rating fatigue scale were compared with those of the multidimensional assessment of fatigue scale. The clinical characteristics of, and the relationships between, fatigue and the conventional core set outcome measures, were defined. Elements of persistent post treatment fatigue not explained by the core set outcome measures were further clarified in a comparative study between two subgroups of patients with good disease outcome and either a poor fatigue outcome or a good fatigue outcome. The qualitative study of patients' perceptions further explored the unique elements of persistent fatigue, and moreover, identified from patients' experiences, and from the literature, potential modifiable factors to improve fatigue outcome.

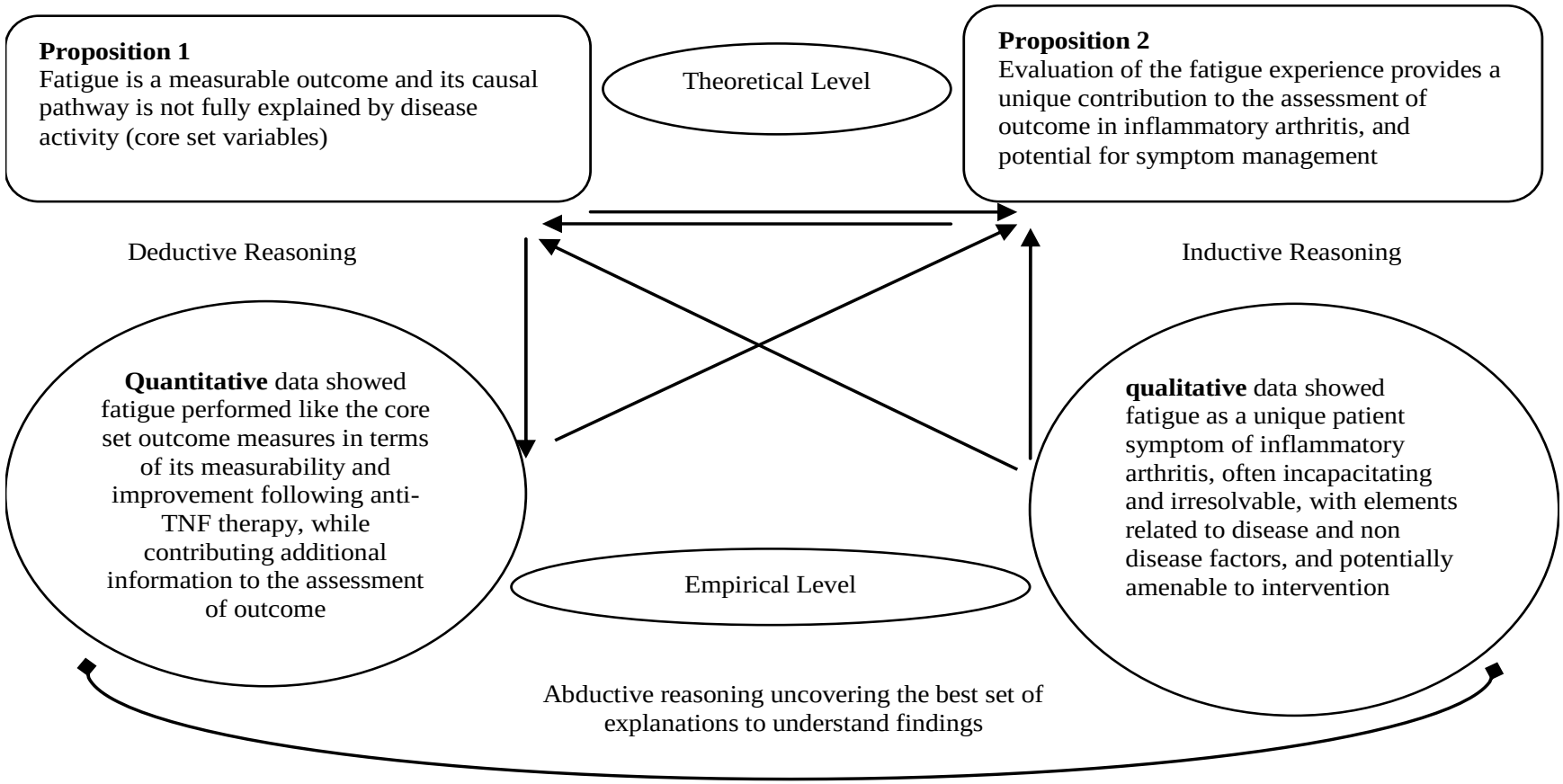
6.2 Combining Quantitative and Qualitative Research Findings

The nature of the identified research problem directed the choice of pragmatism as the underlying research paradigm which supports the use of mixed methodologies in fulfilling the objectives of the study. A collaborative agreement between clinical researchers and

patients previously identified the need to standardise and validate measurement instruments, and explore the meaning of the fatigue experience in patients with inflammatory arthritis. The pragmatic focus was on finding solutions to the research problem, mixing methods of inquiry in order to do so. Principles of deductive reasoning were used to test preceding theories about the relationship between fatigue and measures of inflammation, namely the core set outcome measures. The principal theoretical drive of the study was deductive. However, in order to more fully address the research problem, inductive reasoning was also used arguing from the opposite direction of specific observations in relation to the lived experiences of fatigue. In so doing a basis for future research hypotheses in relation to this patient reported outcome measure was generated. Comprehensive attention to the study objectives required movement between deductive and inductive reasoning in order to uncover the best sets of explanations to understand the study findings; this is the nature of abductive reasoning within a paradigm of pragmatism.

Using an illustrative model, previously proposed, (Erzberger and Kelle 2003; Östlund *et al.* 2011), the complementary quantitative and qualitative findings were integrated as presented in Figure 6-1. Theoretical proposition 1 is supported by the empirical quantitative findings. Qualitative findings supported and complemented the quantitative findings as patients described both disease related and non disease related causes of fatigue. From the empirical qualitative findings, a second and complementary theoretical proposition (proposition 2) can be inferred.

Figure 6-1: Illustration of the use of triangulation on the complementary results



Theoretical propositions, empirical findings from quantitative and qualitative data and the logical relationships between them

Data analysis occurred sequentially; this permitted the quantitative findings to inform the selection of patients for interview in the supplemental qualitative component of study. Discussion of these results served to validate findings on whether fatigue is caused directly by disease activity; contradictions and fresh perspectives were discussed, especially with regard to the relationship between fatigue and either clinician, and/or other patient reported outcomes, dependent on disease state. The additional empirical material helped to develop an explanation of findings, in an attempt to clarify unique elements of fatigue, and provide a basis for effective interventions. In this way, the exploration of patients' experiences of, and management strategies for, fatigue added a dimension of completeness to this study of the poorly understood concept and undermanaged symptom of inflammatory arthritis. This narrative integration of both sets of data added breadth and scope to this study and consequently to the explanation of the study results (Erzberger and Kelle 2003; Östlund *et al.* 2011), and identification of areas for further research.

This discussion represents the meaning of the study observations and findings in light of the previous findings made by other researchers. Principles, relationships, and generalisations, based on the study findings are discussed: moreover, the implications for, and practical application of, the results and findings in real life clinical situations are considered in the following order: -

- Characteristics of patients prescribed TNFi therapy for inflammatory arthritis
- Measurement of fatigue using psychometrically sound tools
- Levels of fatigue in patients with inflammatory arthritis prescribed TNFi therapy
- Explained elements of fatigue: clinical characteristics and inter-relationships
- Unexplained elements of fatigue and clarification of unique contribution
- Fatigue: a patient reported outcome in rheumatoid arthritis amenable to intervention
- Identified potential modifiable factors to improve fatigue outcome
- Study limitations and recommendations
- Main conclusions: what this study adds

6.3 Characteristics of Patients Prescribed TNFi Therapy for Inflammatory Arthritis

6.3.1 Previous studies

This study examined the longitudinal course of fatigue in patients with rheumatoid arthritis and psoriatic arthritis who were prescribed TNFi therapy. Originally, the efficacy of these medications was demonstrated through randomised controlled trials (Furst *et al.* 2002); data are now available on their real life use to treat patients with rheumatoid arthritis and psoriatic arthritis, from national registries such as the British Society for Rheumatology Biologics Register (Saad *et al.* 2009; Saad *et al.* 2010; Hyrich *et al.* 2011), the Danish DANBIO register (Hetland 2005; Hetland *et al.* 2008; Hetland *et al.* 2010), and the south Swedish treatment group register (Kristensen *et al.* 2008; Gülfe *et al.* 2010). The clinical features of rheumatoid arthritis (Furst *et al.* 2008; Hyrich *et al.* 2011), and more recently psoriatic arthritis (Saad *et al.* 2008; Saad *et al.* 2010), have consistently improved since the nineties with the availability and use of TNFi therapies. However, despite spontaneous reports from patients of much reduced fatigue levels following TNFi therapy in clinical practice (Wolfe and Michaud 2004), and in clinical trials (Weinblatt *et al.* 2003; Moreland *et al.* 2006; Strand *et al.* 2009), the debate about fatigue and disease activity as its causal pathway being unsubstantiated, continues (Wolfe *et al.* 1996; Bergman *et al.* 2009; Rasker 2009).

6.3.2 Patient baseline characteristics and response to therapy

The clinical characteristics of this study cohort reflected an active disease state for which treatment with an TNFi therapy was indicated (Smolen *et al.* 2010b). At baseline, defined as time of first dose of TNFi therapy, demographics, as well as disease characteristics, were in keeping with those found in previously published longitudinal observational data. These include a predominately female population, older mean age equivalent of fifty years, mean disease duration of eleven years, and history of previous failure of disease modifying anti-

rheumatic drugs. These characteristics are largely in keeping with the 2001-2008 UK biologics register on patients with rheumatoid arthritis (Hyrich *et al.* 2011), and the 2002-2006 data on patients with psoriatic arthritis (Saad *et al.* 2010). Current study participants had a lower mean baseline HAQ-disability index than published observational studies (Saad *et al.* 2010; Hyrich *et al.* 2011). The majority of patients had a moderate or high disease activity state at baseline; this mean baseline disease activity score (DAS28=4.9) reflected at least a moderate disease activity in keeping with international practice guidelines for prescribing TNFi therapy (Hetland *et al.* 2008; Ng *et al.* 2010). This is lower than that for UK patients with either inflammatory disease (Saad *et al.* 2010; Hyrich *et al.* 2011) where prescribing is regulated by NICE guidelines which recommend a high DAS28 > 5.1 on initiation of therapy (Ledingham *et al.* 2005; National Institute for Health and Clinical Excellence 2007a, 2007b, 2007c).

The observed response to TNFi therapy measured by the DAS28 (Prevoo *et al.* 1995), and the EULAR response criteria (van Gestel *et al.* 1996), were also in keeping with the characteristics and trends found in previously published longitudinal observational data (Saad *et al.* 2010; Hyrich *et al.* 2011). The magnitude of the effect of TNFi therapy on disease activity was seen in the 56% and 61% of patients, 3 and 6-months post baseline, respectively, who achieved either a state of low disease activity (DAS28 ≤3.2), or remission (DAS28 <2.6), on the basis of the DAS28 (Prevoo *et al.* 1995). According to the EULAR criteria (van Gestel *et al.* 1996), over 80% of patients demonstrated a moderate to good response at 3-months, only 14% demonstrated no response. All patients demonstrated a response by 6-months; a moderate disease response was obtained by 40% and a good response by 60% of patients at 6-months. These data represents an overall better disease response when compared with the UK register report which showed that between 20-25% of patients from both of these diagnostic groups achieved no response (Saad *et al.* 2010; Hyrich *et al.* 2011), 6-months post baseline. While mean baseline HAQ scores were lower than those published elsewhere the mean improvement observed 6-months post baseline, reflected published post treatment patterns (Saad *et al.* 2010; Hyrich *et al.* 2011).

Changes in the level of disease activity captured at 3-months and 6-months post baseline, using the objective core set of outcome measures, represented an overall improvement in

disease status over time. This most significant improvement occurred between baseline and 3-month follow-up, and was maintained or further improved at 6-month follow-up. The observed 3 months response time from initiation of treatment is in keeping with previous studies of patients from both diagnostic groups (Heiberg *et al.* 2007; Saad *et al.* 2010; Hyrich *et al.* 2011). Results were in keeping with expert consensus based on evidence from randomised controlled trials that sufficient improvement in symptoms, signs and/ or laboratory measures should be clinically evident within twelve weeks of initiating TNFi therapy, in patients with rheumatoid arthritis (Furst *et al.* 2002; Furst *et al.* 2008). This is also the case for psoriatic arthritis where response within 3 months has been demonstrated in the majority of patients (Eder *et al.* 2010).

6.3.3 Summary

While prescribing of TNFi therapy is guided, if not governed, by professionally agreed guidelines (Ledingham *et al.* 2005; Combe *et al.* 2007; Furst *et al.* 2008; Saag *et al.* 2008; Smolen *et al.* 2010b), variability exists across Europe within protocols for treatment initiation (Emery *et al.* 2009), UK practice is governed by NICE guidelines (Ledingham *et al.* 2005; National Institute for Health and Clinical Excellence 2007b, 2007c, 2007a). The selection process within the site of the current study, used to identify study candidates, was previously shown to be appropriate and in accordance with international best practice, despite the absence of strict national regulation (Ng *et al.* 2010). The selection process, baseline demographics, and disease characteristics, and observed response to therapy, compared well with prescribing recommendations, and previously published longitudinal observational data, from real life clinical settings, on patients with either rheumatoid arthritis (Hyrich *et al.* 2011), or psoriatic arthritis, prescribed TNFi therapy (Kristensen *et al.* 2008; Saad *et al.* 2009; Saad *et al.* 2010), supporting the external validity of study results.

6.4 Measurement of Fatigue Using Psychometrically Sound Tools

This study provides new information on the standardisation and validation of measurement instruments for the evaluation of the subjective experience of fatigue (Kirwan *et al.* 2003). The recommendation that fatigue in inflammatory arthritis should be included as an outcome measure in clinical studies (Gladman *et al.* 2007b; Kirwan and Hewlett 2007; Aletaha *et al.* 2008) requires evidence that measurement instruments used in the evaluation of fatigue, as with all healthcare outcomes, are psychometrically sound (DeVon *et al.* 2007). The accuracy and feasibility of two distinct fatigue scales was evaluated within this detailed assessment of patients with active inflammatory arthritis. Levels or severity of fatigue were quantified using a single dimension 5-point verbal rating fatigue scale; the multidimensional assessment of fatigue scale, as well as quantifying levels, provided a more global evaluation (Nicklin *et al.* 2010a) of other dimensions of the symptom experience.

This longitudinal observational study is the first to report on the use of a single dimension verbal rating (ordinal) scale in the measurement of fatigue in both rheumatoid arthritis, and psoriatic arthritis, following the initiation of treatment. While the literature is replete with reports of the use of single dimension fatigue scales in inflammatory arthritis (Gladman *et al.* 2004; Wolfe 2004; Hewlett *et al.* 2007), the use of a verbal rating scales is less frequent than either visual analogue scales or numeric rating scales, (Wolfe 2004; Hewlett *et al.* 2007; Minnock *et al.* 2009; Minnock *et al.* 2010; Nicklin *et al.* 2010a). Previous longitudinal studies which used a generic verbal rating scale to measure fatigue in rheumatoid arthritis involved more heterogeneous groups in which no treatment intervention was initiated (Pinals *et al.* 1982; Stone *et al.* 1997; Katz 1998). The stability, consistency, and the ability of a verbal rating scale to capture variation in fatigue were previously reported in patients with rheumatoid arthritis (Stone *et al.* 1997); no previous evidence of verbal rating scale in the measurement of fatigue levels in psoriatic arthritis was found (Gladman *et al.* 2004).

This study confirmed the reliability of both scales. The previously reported internal consistency of the global fatigue index, and two subscales, of the multidimensional scale

(Belza *et al.* 1993), was tested and upheld, in the combined diagnostic participants in this study. Cronbach's alpha ranged between 0.88 and 0.95; these are in keeping with those reported by its developer (Tack 1990a; Belza 1995), and satisfying accepted standards of ≥ 0.90 for clinical tools, and ≥ 0.70 for research tools (DeVon *et al.* 2007).

More new information was gained from the comparative analysis of scale psychometric properties. The only similar information in the literature to date reports on the comparative performance of a visual analogue scale with the multidimensional scale in fatigue assessment in rheumatoid arthritis (Wolfe 2004); no previous direct comparison between a verbal rating fatigue scale and the multidimensional fatigue scale was found. Two forms of between scale equivalence reliability (DeVon *et al.* 2007), were demonstrated. Firstly, similar patterns of scoring and agreement were observed across both scales at each time of assessment. The incremental increase in scores on the multidimensional scales was in accord with the increase in fatigue levels on the 5-point verbal rating scale (none, mild, moderate, severe, very severe); incremental increases were an average of 10 units, from 10 through to 50 on the multidimensional scale. Both scales were shown to be at least moderately correlated at the three times assessed (coefficient range 0.74-0.80). The equivalence reliability of both scales in measuring the same attribute was also demonstrated. Good consistency between the verbal rating scale and the two multidimensional subscales, fatigue severity/level and fatigue interference, was further supported by moderately high levels of agreement at the three assessment times (coefficient range 0.54-0.74). Not surprising, the strongest association was seen between the verbal rating scale, and the severity/intensity subscale of the multidimensional scale, as both are concerned with the quantification of intensity/severity of the symptom. The interference subscale is the substantial multidimensional component of this longer fatigue scale which explains the lower correlations between this subscale and the single severity dimension of the verbal rating.

On the whole good inter-scale reliability was demonstrated; the verbal rating scale was moderately well correlated with the overall global fatigue index, which is a composite of both the severity/intensity and the interference subscales on the multidimensional fatigue scale. However, the weakness of the verbal rating scale, is that ordinal level measurement

does not quantify the amount of difference between ranks, for this reason options for statistical analysis are restricted (Polit and Beck 2010a); neither is a comprehensive evaluation of the fatigue experience provided. The longer multidimensional scales were previously shown to be more reliable than single item visual analogue scales (Wolfe 2004), and have more analytical possibilities due to its interval measurement (Polit and Beck 2010a). Nonetheless, this study showed that estimates of reliability between the verbal rating scale and the multidimensional assessment of fatigue scale demonstrated a strong level of stability, and equivalence of results between the scales (DeVon *et al.* 2007), in measuring the phenomenon of fatigue in patients with inflammatory arthritis. Therefore it is a suitable scale for use in daily clinical practice.

Both construct and criterion validity were evaluated in the current study. Face and content validity of a generic ordinal fatigue scale and the multidimensional assessment of fatigue scale in patients with rheumatoid arthritis were previously reported (Hewlett *et al.* 2007) (Section 4.7.2). This study demonstrated the degree to which both scales measured the intended construct (DeVon *et al.* 2007), the phenomenon of fatigue in inflammatory arthritis. Good construct validity was seen between the two fatigue scales and patient reported outcomes, with evidence of convergent validity with pain and the HAQ-disability index; and divergent validity with vigor, measured on the Profile of Mood States, and with self- efficacy for other symptoms, measured on the arthritis self-efficacy scales.

Factor analysis, which identified clusters of related concepts (Polit and Beck 2010a), substantiated the claim that the multidimensional assessment of fatigue scale measures more than one dimension in the domain of fatigue in inflammatory arthritis. Three separate dimension clusters were identified across the three time points; one was interference with activities of daily living, the second was interference with social/leisure/physical activity, and the third was fatigue severity and timing.

A moderate correlation between the verbal rating scale and the gold standard fatigue specific multidimensional scale, confirmed the criterion validity of the 5-point verbal rating scale in measuring the construct of fatigue in these patients with inflammatory arthritis.

These results contribute further valuable evidence on aspects of face, content, construct and criterion validity of the single dimension verbal rating scale, and the multidimensional assessment of fatigue scale in a mixed diagnostic group of patients with rheumatoid arthritis and psoriatic arthritis treated with TNFi therapy.

This study confirmed sensitivity or responsiveness to change following initiation of treatment using three separate change coefficients. This was the third psychometric property of the fatigue scales evaluated; sensitivity to change, as opposed to results from static parameters, defines a good scale (Fitzpatrick *et al.* 1992; Wolfe 2004). Both fatigue scales captured a significant reduction in fatigue levels between baseline and 3-months, and baseline and 6-months. The further change in fatigue levels measured between the 3-month and 6-month time points was found not to reach statistical significance on either scale. These complementary results show that the performance of both scales in relation to sensitivity to change over time was equivalent. Previous studies have demonstrated the sensitivity to change of single item fatigue scales, primarily, visual analogue scales and numeric rating scales in rheumatoid arthritis (Wolfe 2004; Hewlett *et al.* 2007; Minnock *et al.* 2009), and of numeric rating scales in psoriatic arthritis (Minnock *et al.* 2010). This study provides new evidence on the responsiveness of a 5-point verbal rating scale in both rheumatoid arthritis and psoriatic arthritis following treatment initiation; it also confirms the equivalence of both scales in terms of sensitivity to change over time.

Secondly, calculation of the effect size quantified the sensitivity of the multidimensional scales by comparing it with the effect size of the core set outcomes; ordinal scale data is not suitable for effect size calculation. The effect size of the multidimensional fatigue scales was fourth after tender joint count, swollen joint count and global health in terms of its ability to detect change 3-months post initiation of treatment. At 6- months post baseline it was ranked sixth, being superior to the laboratory measure of CRP, only. These findings compare with results from two previous pilot studies that used single item verbal rating scales in these separate disease groups prescribed TNFi therapy (Minnock *et al.* 2009; Minnock *et al.* 2010). Although the multidimensional assessment of fatigue scale was designed and validated for use in patients with rheumatoid arthritis the need for further evidence of its sensitivity to change was recommended (Hewlett *et al.* 2007). This study

provides that evidence on patients with inflammatory arthritis following initiation of treatment. These results confirm the responsiveness of the multidimensional scale across three time points and a variety of disease states and populations.

Findings on sensitivity to change were further supported by a third assessment of responsiveness. Assessment of the comparative sensitivity to change of each of the fatigue scales in the detection of a change in the individual core set outcome measures, and the composite DAS28, highlighted the superiority of the multidimensional assessment of fatigue scales over the verbal rating scale, in terms of responsiveness. At 3-months the multidimensional assessment of fatigue scales, and not the verbal rating scale, was significantly more sensitive to change in pain, global health, HAQ disability index, and DAS28. At 6-months the multidimensional assessment of fatigue scales showed significant sensitivity to patient global health variable, only. A similar finding in relation to single item scales was reported between a visual analogue fatigue scales and the multidimensional assessment of fatigue scales (Wolfe 2004). Knowledge that the verbal rating scale is sensitive to change supports it use in situations where minimal responder and administrator burden is imperative, such as pressurised clinical settings. However, where and when more in-depth knowledge on the symptom experience of fatigue in relation to other variables is required the multidimensional scale was shown to be more responsive.

Feasibility in terms of ease of use, application and interpretability of both scales was examined as an important characteristic of instruments used in outcome research. Frequently, this scale property is what determines scale choice and success of use in the real life situation (Boers *et al.* 1998). The equally good response rate for both scales was taken as evidence of minimal responder burden. Both scales are available free within the public domain which supports their ease of availability and of use. Each scale is designed to be self-administered by patients and can be completed following check in while awaiting their clinical review. In this way data are available to the clinician from the outset of the appointment so aiding efficiency and efficacy of clinical reviews. Interpretation of the single dimension verbal rating scale is immediate and straightforward. Calculation of the score on the multidimensional scale takes up to five minutes to complete. This is perhaps a disadvantage for use in busy clinical practice as a routine screening tool, at the same time it

highlights its feasibility for use in the proactive prevention, and active planning of an individualised management intervention by clinicians. It has also been suggested that the information derived from the subscales offers no additional benefit, and that in practice this scale is reduced to a single dimension score (global fatigue index) (Wolfe 2004). The additional utility of the multidimensional scale is contingent on whether the overall score, the global fatigue index, is interpreted as a single estimate of fatigue or whether the multidimensional information content of the scale is utilised clinically towards the management of this symptom. Unless the latter is the case then it carries an unnecessary responder burden. This study supports the ease of application of both the long and short form fatigue scales. Choice of instrument is dependent on whether the purpose of measuring fatigue is screening only, or screening and tailored management of this symptom, based on the information gleaned from the assessment of the multiple dimensions of fatigue.

These results contribute knowledge on the standardisation, and optimal methods of assessment of fatigue in inflammatory arthritis (Kirwan *et al.* 2005b; Gladman *et al.* 2007b). Comparison of scale psychometric properties confirmed the validity of a single item verbal rating scale. The evidence on sensitivity to change supports the suitability of the verbal rating scale for screening and quantification. The sensitivity to change of the multidimensional scales mirrored that of the core set outcome measures. The multidimensional scale was shown to be more responsive than the verbal rating scale when more in-depth knowledge on the symptom experience of fatigue in relation to the core set outcomes is required. This suggests that a multidimensional scale is the instrument of choice for the comprehensive assessment of the symptom of fatigue, and of interventions, in the management of this complex phenomenon in patients with inflammatory arthritis. By contrast, a verbal rating scale is a more feasible scale as it can be used anywhere and anytime, and without the need to have an instrument to hand.

What is important is that fatigue assessment occurs, is documented and, moreover, responded to by the assessing clinician. This longitudinal observational study provides evidence on the validation of a 5-point verbal rating scale in the assessment of fatigue outcome in rheumatoid arthritis and psoriatic patients. It contributes important information

on the psychometric properties of fatigue instruments for use in health care outcome research.

6.5 Levels of Fatigue in Patients with Inflammatory Arthritis Prescribed TNFi Therapy

A longitudinal evaluation of the clinical characteristics of fatigue was undertaken. The use of two separate measurement scales in evaluating optimal methods of assessment acknowledged the fact that the phenomenon of fatigue in inflammatory arthritis is a multidimensional experience (Tack 1990a; Hewlett *et al.* 2005b; Repping-Wuts *et al.* 2008a). Insight into the interrelationships between fatigue and the conventional core outcome measures, and clarification on unique elements of this phenomenon unexplained by these outcome measures, was sought.

Over seventy-five percent of patients reported moderate to very severe fatigue levels, prior to initiation of TNFi therapy on the verbal rating scale. Comparable high levels of fatigue (mean $\geq$ 27, scale range 1-50) were captured by the multidimensional scale in more than seventy percent of patients at baseline. These reflect high fatigue level when compared with the reported general population mean of between 16-17, approximately, (Belza 1995); population means are equivalent to the rating of mild fatigue in this current study cohort. A trend towards higher baseline fatigue in patients with rheumatoid arthritis initiating TNFi therapy as opposed to traditional synthetic disease modifying drugs was reported previously in an TNFi treatment response study which included fatigue as a primary outcome (Pollard *et al.* 2006). As TNFi therapy is primarily prescribed when disease activity is resistant to traditional synthetic biologic agents, these study groups represent patients with most severe disease (Heiberg *et al.* 2005). Therefore, findings from this and previous studies demonstrate the association between elevated fatigue levels and a state of disease activity.

Three months post baseline the majority of patients reported either none or mild fatigue. Like the verbal rating scale the multidimensional scale also captured the more substantial and significant improvement in fatigue levels observed at three months. This too is in keeping with previous findings (Pollard *et al.* 2006); in terms of outcome in general, it

conforms with the expectation that clinically significant important responses in patient reported outcome measures, should be demonstrated within 12-24 weeks on initiation of TNFi therapies (Furst *et al.* 2008; Furst *et al.* 2011). While this is a documented trend in relation to fatigue (Heiberg *et al.* 2005), three previous smaller studies reported 3-month data only (Pollard *et al.* 2006; Minnock *et al.* 2009; Minnock *et al.* 2010), and most longitudinal observational studies report 6-month and one year data (Saad *et al.* 2010; Hyrich *et al.* 2011), so direct study comparison is not supported.

6.6 Explained Elements of Fatigue: Clinical Characteristics and Inter-Relationships

The inter-relationships between fatigue and the core set outcomes are central to the ongoing debate as to whether fatigue is a primary or secondary symptom of the auto-immune inflammatory process (Pollard *et al.* 2006; Bergman *et al.* 2009). Answers were sought firstly, by further clarification of the explained elements of fatigue and, secondly, by exploration of some of the unexplained elements of the fatigue experience.

Through factor analysis fatigue distinguished itself as a patient factor, representative of the disease, and health status outcome, as distinct from clinical markers of inflammation. Fatigue consistently clustered with the patient reported outcome of pain, global health and the HAQ-disability, as opposed to the clinician derived outcomes (swollen and tender joint count), or biochemically derived measures of outcome (CRP), in inflammatory arthritis. This same link between fatigue and the core set variables was reported in a previous study in patients with both inflammatory and non-inflammatory rheumatic conditions (Bergman *et al.* 2009). Together these findings support the argument against fatigue being solely an inflammatory variable.

However, in the current study high levels of fatigue were demonstrated in parallel with a high composite DAS28, prior to the commencement of treatment. Following initiation of TNFi therapy a consistent fall in fatigue levels occurred in parallel with a reduction in the scores of all the outcome measures, reflecting a parallel clinical improvement in both fatigue and in disease status. This is in keeping with the practice consensus on TNFi (Furst

et al. 2008; Furst *et al.* 2011), and as seen elsewhere in patients with rheumatoid arthritis (Pollard *et al.* 2006), and psoriatic arthritis (Husted *et al.* 2010). The current study confirms the relationship between fatigue and the composite measure of disease activity, over time.

Relationships between fatigue and individual measures of the composite score were next examined. Strong and significant associations were demonstrated between fatigue and the patient reported outcomes, pain, global health, and HAQ-disability index at all time points. More moderate and significant associations with swollen and tender joint count, and CRP, were seen at 3 and 6-months, with tender joint count having a weak but significant association at baseline only. From these findings it is evident that the strength of the relationship between fatigue and individual core variables varied with disease state. However, the stronger relationship seen between fatigue and the patient reported outcomes, pain, global health and disability index, was consistent across all times of assessment.

Variables which explained and predicted fatigue levels at each time point were evaluated though univariate followed by multivariate analysis. It was demonstrated that the variables which exerted the most significant influence on current fatigue levels changed at each time point, along with change in disease state. The set of variables which best explained fatigue during an active disease state prior to the initiation of therapy included a combination of patient reported and biochemical variables, namely, the HAQ-disability index, patient global health, and the acute-phase reactant-CRP. Together they explained a relatively small proportion (28%) of baseline fatigue. With the timely response to therapy seen three months post baseline, and the parallel improvement in disease activity score, pain and tender joint count were the only significant predictors of reported fatigue levels, accounting for 37% of the fatigue experience. While at the 6-months time point 46% of the variance in fatigue levels was explained by patient global health. Improvement in rheumatoid arthritis fatigue was shown previously to be greater with TNFi therapy than with the traditional gold standard synthetic drug, methotrexate (Heiberg 2010). Combined with the current study these data highlight that the association seen between fatigue and other outcomes differs according to state of the disease activity, and confirms the influence this intervention has not only on the core outcomes but also on fatigue outcome. Further, during qualitative interview, patients in this study with persistent post treatment fatigue used descriptions like

the ‘energising’ effect of TNFi therapy, and prior to starting TNFi therapy experiencing ‘fatigue all day’ findings which are in keeping with patient reported benefits to fatigue of TNF-inhibitors (Weinblatt *et al.* 2003; Wolfe and Michaud 2004). These results support the contention that a variety of contributing factors along the causal pathway of fatigue influence the experience of fatigue differently depending on disease state (Hewlett 2007). Therefore different approaches to management are indicated at different stages during the course of these chronic rheumatic diseases.

This study also examined how change in fatigue between assessments was influenced by corresponding changes in the core set variables, following TNFi therapy. Of all the variables the only change variables to make a significant contribution in explaining variance in change in fatigue three months post baseline, when the initial improvement in disease status was captured, were change in HAQ-disability index and global health. Only 15% of the explained variance was accounted for by this significant model. Moreover, it is noteworthy that, at 6-months the explanatory model was non-significant; change in none of the core set outcome measures made a significant contribution to the prediction of change in fatigue when assessed six months post baseline.

Findings related to the explained elements of fatigue raise interesting observations (Table 5-3). It is noteworthy that, 3 months post baseline, as disease activity improved the association between fatigue and swollen and tender joint count, and CRP increased somewhat. One possible explanation for this is the presence of a yet unidentified systemic causal pathway for fatigue during a high disease activity state, where TNFα is implicated, which is not captured by conventional disease outcomes, and that following the institution of therapy resolving peripheral joint symptoms related to swelling and tenderness, and associated pain are then a more direct cause of fatigue. It has been hypothesised that improvement in pain and fatigue associated with chronic inflammation is due to a direct central effect of TNFi therapy on sensory neurons (Pollard *et al.* 2006). Further, results from the multivariate model also implicated an alternate causal pathway during a high disease activity state, as only 28% of baseline fatigue was explained by the core outcomes. Moreover, persistent post treatment fatigue in inflammatory arthritis remained largely unexplained by the conventional core outcome measures.

In practical terms this means that the inclusion of this patient reported outcome as standard along with conventional measures provides additional insight into the overall impact of these chronic inflammatory conditions. The patient reported outcomes most frequently evaluated to date are clinician derived, whereas fatigue which was not assessed in most clinical studies over the last decade (Felson *et al.* 2011a; Felson *et al.* 2011b), has been identified by patients themselves so it is truly synonymous with the patients' perspective (Sanderson and Kirwan 2009). These results confirm that measurement of fatigue in inflammatory arthritis makes an independent contribution to the assessment of disease status, and consequently outcome.

6.7 Unexplained Elements and Further Clarification of Unique Contribution of Fatigue

The magnitude of the unexplained variance in fatigue and also in each of the core set variables was calculated and compared. This showed that all these variables make a unique contribution to the assessment of outcome which is independent of the other variables. Moreover it confirmed that the patient reported outcome least explained by the all the other variables was fatigue, varying between 79-91%; the clinician derived outcome least explained was CRP.

Clarification on the unexplained elements of persistent post treatment fatigue was sought and demonstrated through a more in-depth evaluation of other potential contributory factors, beyond the core set outcome measures. This was undertaken in a comparative component of the study confined to two subgroups of patients with rheumatoid arthritis and good disease response identified six months post baseline. The study group were patients who continued to report persistent post treatment fatigue, and the control group demonstrated a good fatigue outcome. Potential contributing physiological, psychosocial, and behavioural factors such as the multidimensional nature of pain, arthritis self-efficacy, sleep, and mood, were examined.

Firstly, distinguishing characteristics and disease related factors were highlighted between the poor fatigue outcome and good fatigue outcome subgroups. While the subgroups were

matched according to gender, age, disease duration, and disability index, the difference in HAQ-disability scores of 0.35 between the two groups exceeded the known clinical meaningful difference of 0.22 (Pope *et al.* 2009). Although this was not found to be statistically significant, it is noteworthy, as functional health status is repeatedly reported to influence fatigue outcome in rheumatoid arthritis (Pollard *et al.* 2006; Repping-Wuts *et al.* 2007; van Hoogmoed *et al.* 2010). The proportion of patients with poor fatigue outcome who were positive for rheumatoid factor antibody was significantly greater. They also reported significantly longer duration of early morning stiffness, lasting up to three hours, versus between ten and thirty minutes for their counterparts with good fatigue outcome. While the mean DAS28 score (≈ 3.3) reflected a low disease activity state for the poor fatigue outcome group, the even lower DAS28 score for the good fatigue outcome group reflected a clinical remission (DAS28 < 2.6). These data further supports the argument of a direct relationship between fatigue and ongoing inflammation, moreover, assertions that DAS28 < 2.6 is more representative of minimal disease activity than remission (Aletaha *et al.* 2005; Makinen *et al.* 2005; Landewe *et al.* 2006), highlights the need for optimal and judicious disease management for the effective management of all symptoms and overall disease outcome.

Use of the short form McGill pain questionnaire (Melzack 1987), provided more in-depth evaluation of the qualitative as well as quantitative perspective of the multidimensional nature of patients' pain experience. This study confirms that patients with poor fatigue outcome experienced more pain than patients with good fatigue outcome. The literature consistently supports a link between high pain levels and fatigue (Tack 1990b; Crosby 1991; Wolfe *et al.* 1996; Pollard *et al.* 2006; Zautra *et al.* 2007; Minnock and Bresnihan 2008) in patients with rheumatoid arthritis. Is it noteworthy that examination of the individual components of the scale showed the subgroups in the current study reported no significant difference in how they evaluated the 'affective' dimension of pain. However, significant differences between the sensory component of pain; pain intensity over the last week, and current pain intensity were consistent between groups. These finding suggest that the physiological pain experience dominated, with little influence from any emotional or psychological component on the overall symptom experience. One small observational study of patients prescribed TNFi therapy which concluded that fatigue in rheumatoid

arthritis reflected pain and not inflammation also suggested depression as a mediating factor (Pollard *et al.* 2006). There is a risk that the causal contribution of pain to the symptom of fatigue is minimised by literature which highlights the mediating effect of depressive symptoms and mood disorders (Huyser *et al.* 1998; Fifield *et al.* 2001; Jump *et al.* 2004) on the fatigue experience. This study confirmed that the physiological pain experience of intensity/severity as opposed to any affective dimension was more implicated in the causal or explanatory model for those experiencing persistent fatigue.

Along with pain, self-efficacy towards coping with rheumatoid arthritis has been shown previously to influence the explanation of fatigue (Riemsma *et al.* 1998). In the current study comparison between subgroups found that self-belief in ability to manage symptoms related to both pain and functioning was found to be the same for both goups. However, patients in the study group had an overall lower self-efficacy in relation to perceived ability to manage 'other symptoms' related to arthritis. Subscales examination showed this composite score was most influenced by the specific question related to poor self-belief in managing arthritis symptoms in order to engage in activities they enjoy. From previous evidence related to patients with rheumatoid arthritis it is known that for each unit increase in baseline self-efficacy other symptoms, there was a corresponding decrease in fatigue levels two years later (Brekke *et al.* 2001). This fatigue outcome study is concerned with providing a basis for effective interventions, and personal coping resources were identified previously as mediators of improvement in rheumatoid arthritis (Sinclair and Wallston 2001). In this regard both pain and self-efficacy, identified as problematic within the poor fatigue outcome subgroup, are potential modifiable contributory factors to fatigue.

The finding that disturbed sleep is a common complaint among patients with all types of arthritis (Luyster *et al.* 2011), including rheumatoid arthritis (Louie *et al.* 2011), was upheld by the current study. Sleep as an influencing factor on persistent post treatment fatigue was compared between the study group and control group. Similar numbers per subgroup (≈ 71%) used sleep inducing medication at the time of assessment. Patients from both the study group and the control group experienced a similarly high global PSQI scores (8 and 7 respectively), greater than 5 being indicative of poor sleep quality. Examination of the raw data from both groups revealed reasons for poor quality sleep during the previous six weeks

to include: from the study group-“tying to get comfortable so knees don’t hurt”; “pain”, “dry mouth”, “pressure on joints causing pain”: and from the control group “bones are extremely sore”; “just can’t sleep well”; “can’t get comfortable...achy in both hips”. These findings correspond with a recent study which demonstrated that joint pain, and limitation due to pain, mediated the association between arthritis and insomnia (Louie *et al.* 2011). While findings from the current study highlight the need for judicious symptom management in all patients with rheumatoid arthritis, moreover, they do not suggest any causal link between persistent post treatment fatigue and sleep quality.

Depressive symptoms and affective disorders are frequently highlighted as predictors and associates of fatigue in rheumatoid arthritis (Fifield *et al.* 1998; Huyser *et al.* 1998; Fifield *et al.* 2001; Jump *et al.* 2004; Wolfe and Michaud 2009). Results from the current study are less definitive. Three separate aspects of psychological or mood status were evaluated, and compared between the respective subgroups. The Profile of Mood States (POMS) (McNair *et al.* 1971) demonstrated no statistical difference between the subgroups. While the Beck Depression Inventory II (BDI-II) demonstrated a statistically significant difference in mean scores between subgroups, total scores were in what is considered to be the mild to moderate range for depression (Beck *et al.* 1961). However, when the patient with a longstanding diagnosis of depression and corresponding high score, (BDI score 35), was removed from the data set of the poor fatigue outcome group the difference between both groups failed to reach statistical significance. In the third measure used, the Beck Hopelessness Scale (BHS) (Nezu 2000), no difference was demonstrated between subgroups. It is also noteworthy that self-efficacy to self-help if feeling blue was significantly lower in the poor fatigue group; while an association between fatigue and depression is recognised in rheumatoid arthritis so too is the existence of a bi-directional causal pathway (Fifield *et al.* 1998; Wolfe and Michaud 2009). A recent single time point study found a steep increase in depressive scores as functional limitation increased (Margaretten *et al.* 2011); clinical trial data of patients with active rheumatoid arthritis prescribed TNFi therapy found that both fatigue and pain had a significant impact on changes in depression status, and that clinical remission improved symptoms of depression (Kekow *et al.* 2011). This study provides no direct causal association between persistent

fatigue and depressive symptoms in patients with rheumatoid arthritis but suggests that enhanced self-efficacy may improve any interrelationship between fatigue and mood.

6.8 Fatigue a Patient Reported Outcome in Rheumatoid Arthritis Amenable to Intervention

The perception of patients was sought for further clarification and insight into the experience of persistent post treatment fatigue. This supplemental qualitative study provided further enlightenment on unique elements of fatigue along with an explanation and refinement of the results from the longitudinal study. Furthermore, potential modifiable factors to improve fatigue outcome were further clarified.

The findings from this component of study supported and complemented those of the longitudinal component of study, as well as earlier studies. Fatigue associated with rheumatoid arthritis was identified as a unique patient reported outcome amenable to intervention. Patients regarded fatigue as a 'standalone' symptom of rheumatoid arthritis: as found previously in a longitudinal follow-up of patients with rheumatoid arthritis (Heiberg 2010). As a symptom it was distinguished from the more classic symptoms of the disease, such as pain and compromised function (Emery *et al.* 2008), and regarded as another individual component of rheumatoid arthritis. The uniqueness of fatigue as a primary symptom of rheumatoid arthritis was identified in the first qualitative study of this phenomenon ever undertaken (Tack 1990a). In this current study patients worked through disentangling the nature of this symptom and in so doing it was apparent that the fatigue of rheumatoid arthritis was neither a stress nor depressive mood response but more an unrecognised 'classic' symptom of the disease. This perception was the same among patients regardless of variation in disease duration. In other recent studies, UK and Dutch patients', whose participants had similar disease characteristics to patients in this study (gender, age, disease duration and fatigue levels), a distinction was made between the fatigue experience of rheumatoid arthritis and normal or explainable fatigue (Hewlett *et al.* 2005b; Repping-Wuts *et al.* 2008a).

The earliest definition of remission in rheumatoid arthritis, derived from expert case analysis, listed the absence of fatigue as a criterion (Pinals *et al.* 1982), and qualitative studies concur on aspects related to meaning, consequences and management of the symptom (Tack 1990a; Hewlett *et al.* 2005b; Repping-Wuts *et al.* 2008a; Nikolaus *et al.* 2010b). Nonetheless, its utility as an outcome measure is still not clarified or universally accepted, and intervention is seldom considered. On account of the continued lack of recognition of fatigue as a classic symptom of rheumatoid arthritis some patients in this study still reported never being asked about or advised about fatigue in a way they would be about other symptoms such as pain and function. While this finding corroborates with previously reported patients experiences (Hewlett *et al.* 2005b; Repping-Wuts *et al.* 2008a), it emphasis the ongoing lack of recognition of the distinctiveness of this patient reported symptom in rheumatoid arthritis, which has negative implications for its effective management. The lack of 'unique' status for this symptom alongside, and independent of the core outcome measures, results in inadequate assessment, and measurement. Furthermore it deprives patients of permission to discuss this symptom openly, only doing so when it reaches an incapacitating state (IV9:2).

Plausible causal factors for fatigue, from the patients' perspectives, focused mainly on generally recognised and previously identified contributors to fatigue (Tack 1990b; Wolfe *et al.* 1996; Hewlett *et al.* 2005b; Pollard *et al.* 2006); these included pain, both acute and chronic, disease flare, joint damage, reduced dexterity and personal situations. Patients suggested that the lifestyle adaptations imposed by the chronic nature of rheumatoid arthritis, such as alterations to career path, poor health status for retirement years, and co-morbidities, as factors which could exert an influence on the experience and reporting of fatigue. Recently, young women with rheumatoid arthritis who fulfill multiple daily roles were identified as being most vulnerable to the negative impact of fatigue (Nikolaus *et al.* 2010b). The potential for such disease imposed lifestyle adaptations to negatively influence the fatigue experience is documented in a model for the management of unpleasant symptoms developed around fatigue (Lenz *et al.* 1997). Further, such multiple causal factors are encompassed within a recently proposed conceptual framework for rheumatoid arthritis fatigue. This empirically derived framework incorporates the interactive

relationship between three main factors, namely, disease processes, cognitive and behavioural issues, and personal life issues (Hewlett *et al.* 2011b).

In the current study patients experienced fatigue as an incapacitating state impossible to ignore; this is largely in keeping with previously published studies (Tack 1990a; Hewlett *et al.* 2005b; Repping-Wuts *et al.* 2008a). Descriptors patients used emphasised the abnormal and persistent nature of an ordinarily universal symptom (Tiesinga *et al.* 1996). These descriptors were in keeping with those recently identified during a collaborative development of a new fatigue scale with patients (Nicklin *et al.* 2010b). Fatigue exerted a negative effect on participation as defined, in broadest terms, by involvement in life situations (Escorpizo *et al.* 2007). Fatigue was bothersome to patients having interfered with work, domestic, home, social, and leisure activities. When present it reduced patients' capacity for both cognitive and physical performance. In its own right fatigue was experienced as a disabling symptom. Emotionally it contributed to low mood and feelings of frustration. Low mood was a consequence of fatigue and not a cause in the experience of this group of patients; this again highlights the recognised bi-directional nature of the causal pathway between fatigue and depressive symptoms (Wolfe and Michaud 2009). The inexplicable nature of this symptom further supports the case for its unique identity. Perhaps the reported incongruity between the explained and unexplained nature of fatigue is due in part to the well recognised and documented unpredictable disease course that is rheumatoid arthritis (Emery *et al.* 2008). It is the recognised multiple contributory factors which serve as a challenge to its effective management, while at the same time providing multiple opportunities for fatigue interventions (Hewlett 2007).

As in previous studies different practices by patients in relation to the management of fatigue were uncovered. These were largely based on patients' own life experience and included the use of techniques of pacing and relaxation and social supports, all previously reported strategies (Tack 1990a; Hewlett *et al.* 2005b; Repping-Wuts *et al.* 2008a). Moreover, patients reiterated the importance of acknowledging fatigue as a distinct symptom of rheumatoid arthritis; this was advocated by patients as an important proactive step to help fatigue management. The need for both parties in healthcare, that is, patients and health professionals alike to openly acknowledge fatigue as a distinct symptom of

rheumatoid arthritis was both implicit and explicit in relation to effective management of this patient reported health outcome. This is a noteworthy finding particularly as a recent study showed that communication in relation to fatigue occupied as little as 6% of the overall consultation time, and twice more likely to be discussed with the nurse specialist than with the consultant rheumatologist (Repping-Wuts *et al.* 2009b). While this might be the case, evidence from the last two decades found that fatigue had not been included as a primary outcome where care for patients with rheumatoid arthritis was nurse led (Ndosi *et al.* 2011).

6.9 Identified Potential Modifiable Factors to Improve Fatigue Outcome

The provision of a basis for effective interventions to minimise the symptom experience, through integration and interpretation of findings, was a study objective. Potentially modifiable factors suitable for interventions in clinical practice were derived from the data as well as from patients' experiences and recommendations. These key areas include disease related factors such as disease status, characteristics and consequences as well as more specific symptom related factors such as symptom ambiguity and lack of recognition.

6.9.1 Disease status and characteristics

Subsets of patients more at risk of fatigue, such as those with recognised unfavourable disease characteristics and status (Smolen *et al.* 2010b), require early identification and recognition, for example, patients with a positive rheumatoid factor, elevated disability index, DAS28 score greater than the remission cut off score of 2.6. Furthermore, remission as assessed by the DAS28 is more recently regarded as representative of a low disease activity than remission (Felson *et al.* 2011a; Felson *et al.* 2011b), which has implications for optimal disease outcome and symptom management. Further, it highlights the importance of patient reported outcomes versus clinical measures alone in the evaluation of disease status. As demonstrated patients with active disease experience multiple symptoms concurrently, including fatigue. Early intervention not only requires appropriate pharmacological treatment it should also include, as recommended, early adjuvant therapies

including information and education on symptom management, self-management and coping strategies (Combe *et al.* 2007). Access to multi-disciplinary interventions is recommended in order to ameliorate both short and long-term consequences of these chronic conditions (Combe *et al.* 2007; Sanderson and Kirwan 2009). Patients who fail to reach a state of remission are not only at risk of ongoing joint damage but also of the recognised symptom of pain and the less well recognised symptom of fatigue, as part of an active disease state. Optimal disease management is indicated for total symptom amelioration.

6.9.2 Disease consequences

Rheumatoid arthritis and psoriatic arthritis are chronic disease entities, with multiple and variable consequences, these can be short, and /or long term. As this study confirms, the course of fatigue has been shown to vary, therefore, different approaches to symptom management are indicated for different disease states. In the current study successful transfer of learnt pain management skills was reported to be a beneficial skill set for fatigue management by a patient who experienced persistent fatigue. Enhancement of patient self-efficacy towards overall arthritis symptom management should be inculcated early into disease management strategies. The recognised unpredictable nature of inflammatory arthritis (Emery *et al.* 2008), and the recently identified unpredictable and inexplicable nature of rheumatoid arthritis related fatigue (Hewlett *et al.* 2005b; Repping-Wuts *et al.* 2008a; Nikolaus *et al.* 2010b), a finding also of this current study, highlights the need to equip patients diagnosed with these chronic conditions with appropriate self-management skill sets and strategies (Younger *et al.* 2008). Similar interventions, such as core pain management skills, may be affective in relieving more than one symptom (Lenz *et al.* 1997).

6.9.3 Symptom ambiguity

The ambiguity in relation to causal pathways for fatigue in inflammatory arthritis, and the absence, until recently, of a conceptual model for fatigue in rheumatoid arthritis has

contributed to much uncertainly in relation to its nature, methods of assessment and proactive management (Hewlett *et al.* 2011b). Fatigue, ordinary fatigue, is a universal symptom, experienced by most people at some time or other. Reports suggest that approximately 10% of the US population experience fatigue (≥ 1 month duration) (Reyes *et al.* 2003); and a Dutch study showed that up to 25% of a working population report experiencing fatigue, ordinarily (Bültmann *et al.* 2002). Fatigue in rheumatoid arthritis has been shown to encompass explained and unexplained elements. As demonstrated in this study and previously, 'fatigue', the symptom of rheumatoid arthritis, is described by patients as being of an 'extra' ordinary nature. (Tack 1990a; Hewlett *et al.* 2005b; Repping-Wuts *et al.* 2008a). The recently proposed conceptual model for rheumatoid arthritis fatigue which suggests the inter-relationship between three main factors; disease processes, cognitive and behavioural issues, and personal life issues, provides a degree of much needed clarification. This change of status, from one of ambiguity to one of certainty in terms of symptom acknowledgement and recognition of its utility as an outcome, is grounded in internationally endorsed empirical evidence (Kirwan *et al.* 2005b; Kirwan and Hewlett 2007; Kirwan *et al.* 2007; Minnock and Bresnihan 2008; Minnock *et al.* 2009; Minnock *et al.* 2010). While the proposed conceptual model (Hewlett *et al.* 2011b) provides a framework for defining future research projects, moreover, it endorses a more pro-active and holistic, clinical approach to symptom assessment and management. The current study contributes to the standardisation of fatigue measurement in inflammatory arthritis and its establishment alongside the other recognised outcome measures in rheumatoid arthritis.

6.9.4 Lack of recognition

This study confirms it is the lack of recognition of fatigue as a unique outcome in inflammatory arthritis, also previously reported (Hewlett *et al.* 2005b; Repping-Wuts *et al.* 2008a), which contributes to the exacerbation of the symptom experience. In the current study and in previous qualitative studies, patients have verbalised two modifiable factors (Hewlett *et al.* 2005b; Repping-Wuts *et al.* 2008a). Firstly, the experience of little direct intervention or advice from health care professionals on fatigue management, and secondly, the belief that they have to manage this symptom alone, as it is part of their disease.

International recommendations to include fatigue measurement in outcome assessment in clinical trials (Gladman *et al.* 2007b; Kirwan and Hewlett 2007; Aletaha *et al.* 2008), have raised the profile of fatigue. However, physicians in clinical practice recently reported their tendency to pay attention to fatigue on first consultation only, and assume that the patients will raise the issue thereafter (Repping-Wuts *et al.* 2008b). Furthermore, the current study demonstrated that patients too entered this conspiracy of silence in relation to non disclosure or discussion of this symptom, for varied reasons. Symptom management in rheumatology practice is the remit of the multidisciplinary team in an effort to influence the immediate and long term consequences of these chronic diseases (Sanderson and Kirwan 2009). Fatigue has received the endorsement of the international rheumatology community as a patient reported outcome (Kirwan and Hewlett 2007; Aletaha *et al.* 2008). Collaborative and comprehensive symptom assessment using standardised measurement scales, and discussion with patients, on an ongoing basis, seems a rational first step in effective management of fatigue.

6.10 Summary

This study identified more modifiable than non-modifiable factors to improve fatigue outcome. One non-modifiable clinical characteristic shown to be significantly associated with poor fatigue outcome, 6-months post baseline, and again in the comparative study was a positive rheumatoid factor status, a recognised poor prognostic indicator (Emery *et al.* 2008; Smolen *et al.* 2010b). Modifiable factors which distinguished the poor fatigue outcome group from the good fatigue group were longer duration early morning stiffness and a DAS28 score which represented a state of low disease activity (Prevoo *et al.* 1995), as opposed to the state of remission (Fransen *et al.* 2004), seen in the good fatigue outcome subgroup; these differences were statistically significant. Another distinguishing feature was a poorer functional status according to the HAQ-DI; a difference of clinical if not statistical significance (Pope *et al.* 2009). Apart from rheumatoid factor status these are all potentially modifiable factors. Other modifiable factors identified in the current study are among known problematic stressors associated with rheumatoid arthritis (Katz 1998); they relate to pain and disturbed sleep, depressive symptoms, the demand for self management

skills to deal with the multiplicity of arthritis symptoms, and coping and adaptive responses required to master the unpredictability and chronicity of inflammatory arthritis.

This study proposes fatigue as a unique symptom of rheumatoid arthritis which affects outcome, based on both the quantitative results and qualitative findings. Moreover, the acknowledgement of fatigue as an independent outcome alongside the conventional core outcomes of rheumatoid arthritis would help to improve the proactive management of this symptom, and overall patient outcome.

6.10.1 Study Limitations and Recommendations

The purpose of this mixed methods study was to determine the clinical characteristics of, contributory actors to, and unexplained elements of fatigue in patients with rheumatoid arthritis and psoriatic arthritis from both a clinical and patient perspective, to inform practice by providing information on measurement, as well as a basis for effective interventions and management strategies. This study had strengths and weaknesses.

6.11 Study Limitations

Study weaknesses in relation to sampling, data collection and analysis are highlighted. The study was undertaken in a single site academic rheumatology centre that may have unique aspects in service and treatment provision which limits the representativeness of the study findings, nationally or internationally. Information was not collected on factors such as time to diagnosis and/or treatment from onset of symptoms, nor on whether participant had early or established disease. Nonetheless, patient demographic and clinical disease characteristics were in keeping with other studies on patients' prescribed TNFi therapy for an active inflammatory arthritis (Saad *et al.* 2010; Hyrich *et al.* 2011). The limited timeframe of the study imposed a restriction on the number of patients that could be recruited; this was further reduced by the number of eligible patients who declined participation (19%). However, the demographic and clinical characteristics of this group did not differ from those that consented to participate. Further patients were lost to study attrition (13%). This was a longitudinal study conducted in a real life clinical situation and

while the numbers recruited were sufficient for statistical needs a larger sample size would have been preferred. The loss of 33% of the sample at 6-month follow-up is an acknowledged study limitation. Minority groups were not part of the inclusion criteria due their small incidence, therefore results may not be transferable to other specific patient populations.

The study group of patients with inflammatory arthritis comprised of two separate disease entities, namely, rheumatoid arthritis and psoriatic arthritis; while these conditions have many commonalities in relation to patient reported symptoms and approaches to management, unique aspects of these respective diseases may have been overlooked. The number of patients recruited with rheumatoid arthritis and psoriatic arthritis reflected the proportion of each diagnostic group within the clinical service; this is approximately 2.5:1. Therefore the recruitment of equal numbers of patients with both diagnoses was not feasible within the confined two year timeframe for recruitment.

In order to ensure adequate numbers of patients, selection for the second component of study was confined to the larger rheumatoid arthritis cohort of patients. Only 28 patients satisfied the *Poor Fatigue Outcome* criteria so limiting the sample size of each subgroup. Further, the comparative study of persistent post treatment fatigue was restricted to the single disease entity of rheumatoid arthritis. While a high response rate was achieved the generalisation of results of this section to patients with psoriatic arthritis is not appropriate. Similarly, selection of patients for the qualitative component of study was confined to this larger rheumatoid arthritis cohort. The intent of the purposive sampling technique used was selection of informants with the experience of the phenomenon of interest, persistent fatigue. While this receives criticism for being a biased form of sampling it fulfilled the goal of qualitative research in securing participants deemed information-rich for the study purpose.

The use of two separate measurement scales acknowledged the fact that the phenomenon of fatigue in inflammatory arthritis is conceptualised as a multidimensional experience and contributed valuable information on the reliability, validity, sensitivity and feasibility of both scales in the measurement of the complex phenomenon of fatigue following initiation

of treatment. However, some weakness in relation to the ease of use and scoring of the multidimensional scale were identified as a previously observed trend in patient response was noted (Wolfe 2004). Instructions on the multidimensional scales advise patients 'for activities you don't do, for reasons other than fatigue (e.g. you don't work because you are retired) check the box'. The items for which this exclusion check box was used most frequently included work, sexual activity and exercise across the three time points. It is suggested that fatigue may be a reason for non engagement in these predominately physical activities and that this is not captured by this scale (Wolfe 2004). While this tick box option was used by patients frequently a tendency to use neither the tick box option nor the numeric rating scale was observed; the location of the tick box is such that it is easily overlooked as a response option making interpretation and scoring difficult. Conflicting guides to scoring exist in the literature (Wolfe 2004; Hewlett *et al.* 2007); this study used the score range of 1-50 according to the original developers guidelines (Multidimensional Assessment of Fatigue 1990).

Other potentially important contributory factors to fatigue were not examined, such as co-morbidities; body mass index; and illness perceptions; unidentified physiological mechanisms.

No claim is made that the findings from the qualitative content analysis are representative of the experience of all patients with persistent post treatment fatigue as this is not the purpose of qualitative research. However, they can be utilised to inform the management of fatigue in patients in a similar context and to inform future research and practice. Qualitative content analysis is the least interpretative of qualitative analysis approaches; therefore, while these study findings are an end product in themselves, more especially they serve as entry points for further research.

6.12 Recommendations for Further Research

Areas appropriate for further research with fatigue a primary outcome include:

1. Prospective, longitudinal studies of homogenous patient groups in relation to diagnosis, disease state (early and established disease) and treatment intervention.
2. Studies to differentiate between primary fatigue and secondary fatigue, and between predictors of fatigue during different states of disease activity.
3. Testing of interventions to enhance self-efficacy in relation to the management of the multiple concurrent symptoms of inflammatory arthritis, such as fatigue, pain and functional limitation.
4. Randomised controlled studies to test the impact of early adjuvant self-management interventions for fatigue and symptom management in inflammatory arthritis.
5. Testing of non-pharmacological interventions such as dynamic exercise, hydrotherapy, occupational therapy and cognitive behavioural techniques in promoting healthy lifestyle behaviours in patients with chronic rheumatic diseases.
6. Testing of the benefits of multidimensional assessment of fatigue in the planning of tailored collaborative pharmacological and non-pharmacological interventions.

6.13 Recommendations for Clinical Practice

Improved collaborative management of fatigue in inflammatory arthritis can be provided based on the following recommendations for clinical practitioners:

1. Symptom acknowledgement: Clinical practitioners need to acknowledge fatigue as a classic symptom of inflammatory arthritis from time of diagnosis. Just as swollen and tender joints and pain are openly discussed with patients as evidence of active disease so too should the symptom of fatigue. In this way recommended adjuvant interventions for the comprehensive management of inflammatory arthritis, such as patient information and education programmes on symptom coping and management can be implemented and self-management strategies developed (Combe *et al.* 2007). Moreover, patients should be facilitated to report and discuss this symptom as an indicator of disease state and change in disease state. Fatigue needs to be included in a proactive and timely approach to symptom management in order to improve outcome.
2. Symptom assessment: Early and repeated measurement of fatigue is indicated using scales feasible for use in a busy clinical practice. This must be followed by an open collaborative approach with patients to symptom management. Patients with persistent post treatment fatigue require multidimensional assessment of impact and coping in order to identify modifiable factors.
3. Proactive symptom management: In rheumatology clinical practice symptom management is the remit of the multidisciplinary team. Tailored symptom management should encompass the recognised influencing factors of fatigue including the disease process, cognitive and behavioural factors and personal life issues (Hewlett *et al.* 2011b).
4. Fatigue risk factors: Identification of patients more at risk of experiencing persistent fatigue such as patients with ongoing disease activity, greater pain, and disability, for the purpose of optimising both pharmacological and non-pharmacological interventions in accordance with EULAR guidelines (Combe *et al.* 2007).
5. Self-management strategies: Patient education on generic self-management strategies should be a core part of adjuvant therapy introduced from time of diagnosis.
6. Enhance arthritis self-efficacy: Patient education and cognitive interventions to enhance self-efficacy for arthritis symptom management.

6.14 Main Conclusions: What This Study Adds

- The validity of both a single dimension verbal rating scale and the multidimensional assessment of fatigue scale in measuring fatigue in inflammatory arthritis were upheld; psychometric properties were comparable; the multidimensional scale demonstrated superior sensitivity in detection of change in the individual core set variables.
- Fatigue changed in parallel with the other clinical measures of disease activity over time following initiation of TNFi therapy.
- Initiation of TNFi therapy resulted in an effect size for fatigue of 23%; this small effect size was greater than that for CRP and similar to that for pain and HAQ.
- The predictors of current fatigue levels varied with current disease status; significant baseline predictors were HAQ, global health and CRP; 3-month predictors were pain and tender joint count; the 6-month predictor was global health.
- Change in fatigue levels in patients established on TNFi therapy was best explained by changes in HAQ-disability index and global health.
- A large percentage (91%) of persistent post treatment fatigue was not explained by the core set-variables.
- In patients with rheumatoid arthritis who achieved a good disease response those who demonstrated poor fatigue outcome experienced more pain and low self-efficacy for symptoms other than pain and function, without any significant negative contribution from sleep or mood, when compared with those who demonstrated a good fatigue outcome.
- Fatigue was identified by patients as a unique outcome in rheumatoid arthritis, amenable to intervention.
- Potential modifiable factors identified include poor symptom acknowledgement and assessment for the purpose of improving overall disease outcome and health status.
- Potential proactive interventions include early recognition of at risk patient subsets, optimal disease management guided equally by patient reported and clinician derived outcomes, patient education to enhance self-efficacy for arthritis symptom management.

6.15 Recommendations for Nursing Practice

Symptom management, along with structured patients education and support services have been named by Irish rheumatology nurses as core to their expanded practice remit (Minnock 2008). However, like their Dutch and UK counterparts (Repping-Wuts *et al.* 2009a) finding from this study confirm the need to improve nurses engagement with patients on the symptom of fatigue for the purpose of enhanced management and heath outcome. Based on the evolving empirical evidence related to fatigue in inflammatory arthritis steps which need to be taken in this regard include:

1. Introduction into all undergraduate and post graduate nurse education programmes the concept of fatigue as a recognised classic symptom of inflammatory arthritis alongside the traditional triad of painful swollen and hot joints.
2. Skills education for nurses to improve communication, screening, assessment and ongoing monitoring and dialogue around this symptom with patients and the wider healthcare team.
3. Skills training in strategies for self-management, and cogitative behavioural approaches (Hewlett *et al.* 2011a) for all nurses working at specialist and advanced practice level in rheumatology.
4. Engagement with patients as education and research partners in raising awareness and trialling management strategies for this symptom by nurse clinicians and practitioners in rheumatology, and educators and researchers in chronic disease.

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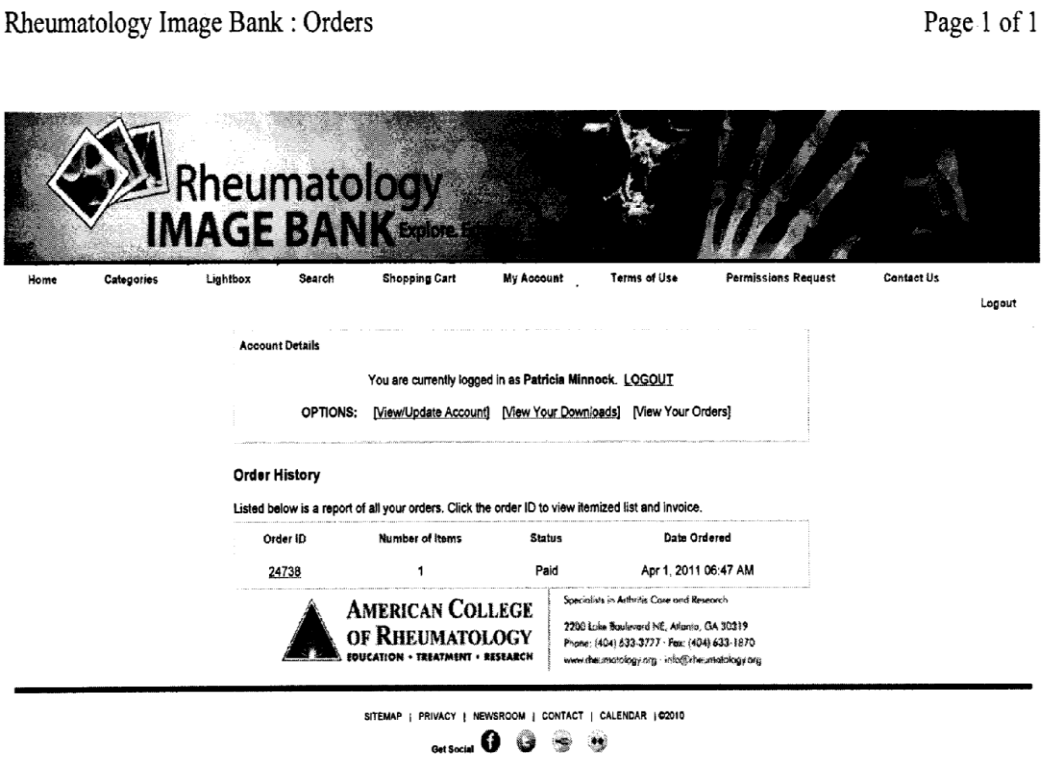
APPENDICES

Appendix 1: ACR Image Bank permission request (Figure 3-1)



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From: Boer de, Ingrid, Springer SBM NL [mailto:Ingrid.deBoer@springer.com]

On Behalf Of SpringerImages Permissions
Sent: 06 January 2011 10:25
To: Patricia Minnock
Subject: RE: SpringerImages Requesting Copyright Permission

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With kind regards,

_____
Ingrid de Boer (Ms.)
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_____
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Appendix 3: CASPAR and original diagnostic criteria for psoriatic arthritis

CASPAR criteria for psoriatic arthritis consist of inflammatory articular disease (joint, spine, or entheseal) with >/= **3 points** from the above categories.

The sensibility is 98.7% and the specificity is 91.4%.

1. Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis **(2 points)**
    a. Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist.†
    b. A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified health care provider.
    c. A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to patient report.
2. Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination **(1 point)**
3. A negative test result for the presence of rheumatoid factor by any method except latex **(1 point)**
4. Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist **(1 point)**
5. Radiographic evidence of juxta-articular new bone formation appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot **(1 point)**

† Current psoriasis is assigned a score of 2; all other features are assigned a score of 1.

Brent LH.Inflammatory arthritis: an overview for primary care physicians.Postgrad Med. 2009 Mar;121(2):148-62.
Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H; CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006 Aug;54(8):2665-73.
Helliwell PS, Taylor WJ. Classification and diagnostic criteria for psoriatic arthritis. Ann Rheum Dis. 2005 Mar;64 Suppl 2:ii3-8.

DIAGNOSTIC CRITERIA FOR PSORIATIC ARTHRITIS

Original diagnostic criteria for psoriatic arthritis (Moll and Wright 1973b)

1	An inflammatory arthritis; peripheral arthritis and / or sacroilitis or spondylitis
2	The presence of psoriasis
3	The (usual) absence of serological tests for rheumatoid factor

Appendix 4: BMJ Publishing Group permission-EULAR algorithm (Table 3:9)

From: Copyright Clearance Center [mailto:rightslink@marketing.copyright.com]
Sent: 30 January 2011 20:21
To: Patricia Minnock
Subject: Thank you for your Rightslink / BMJ Publishing Group Ltd. order

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Order Details
Licensee: Patricia Minnock
License Date: Jan 30, 2011
License Number: 2598930925005
Publication: Annals of the Rheumatic Diseases

Title: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs

Type Of Use: Thesis/Dissertation
Total: 0.00 EUR
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Invoices are issued daily and are payable immediately upon receipt.
To ensure we are continuously improving our services, please take a moment to complete our customer satisfaction survey.

Appendix 5: BMJ Publishing Group permission-GRAPPA guidelines (Figure 3-3)

Springer Image Permission

From: [redacted]

Sent: 30 January 2011 21:36

To: Patricia Minnock

Subject: Re: SpringerImages Requesting Copyright Permission

Dia duit

That sounds great. Good luck!

Best regards to Professor [redacted]

From: Patricia Minnock

Sent: Sunday, January 30, 2011 12:54 PM

To: [redacted]

Subject: FW: SpringerImages Requesting Copyright Permission

Dear Professor [redacted]

As requested, I wish to inform you that I have obtained permission to use Figure 1. GRAPPA treatment guidelines for psoriatic arthritis, categorised by disease characteristics and distinct organ involvement, from Kavanaugh A, Ritchlin C, and the GRAPPA Treatment Guideline Committee. Systematic review of treatments for psoriatic arthritis: an evidence based approach and basis for treatment guidelines.

J Rheumatol 2006;33: 1417-56, within my doctoral thesis on fatigue in patients with inflammatory arthritis.

I am a PhD clinical fellow at Trinity College Dublin, my clinical supervisor is Professor [redacted]

With thanks

Yours sincerely

Patricia

Appendix 6: American College of Rheumatology recommendations of specific ways to assess each disease activity measures in the core set

*(Felson *et al.* 1993)

Disease activity measure	Method of assessment
Tender joint count †	ACR tender joint count (see ref. 47), an assessment of 68 joints. The joint count should be done by scoring several different aspects of tenderness, as assessed by pressure and joint manipulation on physical examination. The information on various types of tenderness should then be collapsed into a single tender-versus-non-tender dichotomy.
Swollen joint count ‡	ACR swollen joint count (see ref. 47), an assessment of 66 joints. Joints are classified as either swollen or not swollen.
Patient's assessment of pain	A horizontal visual analog scale (usually 10cm) or Likert scale assessment of the patient's current level of pain.
Patient's global assessment of disease activity	The patient's overall assessment of how the arthritis is doing. One acceptable method for determining this is the question from the AIMS instrument: "Considering all the ways your arthritis affects you, mark 'X' on the scale for how well you are doing." An anchored, horizontal, visual analog scale (usually 10cm) should be provided. A Likert scale response is also acceptable.
Physician's global assessment of disease activity	A horizontal visual analog scale (usually 10cm) or Likert scale measure of the physician's assessment of the patient's current disease activity.
Patient's assessment of physical function	Any patient self-assessment instrument which has been validated, has reliability, has been proven in RA trials to be sensitive to change, and which measures physical function in RA patients is acceptable. Instruments which have been demonstrated to be sensitive in RA trials include the AIMS, the HAQ, the Quality (or Index) of Well Being, the MHIQ, and the MACTAR.
Acute-phase reactant value	A Westergren erythrocyte sedimentation rate or a C-reactive protein level.

* ACR = American College of Rheumatology (formerly, the American Rheumatism Association); AIMS = Arthritis Impact Measurement Scales; HAQ = Health Assessment Questionnaire; MHIQ = McMaster Health Index Questionnaire; MACTAR = McMaster Toronto Arthritis Patient Preference Disability Questionnaire.

† The 68 joints to be examined for tenderness are: temporomandibular (n = 2), sternoclavicular (n = 2), acromioclavicular (n = 2), shoulder (n = 2), elbow (n = 2), wrist (n = 2), metacarpophalageal (n = 10), interphalangeal of thumb (n = 2), distal interphalangeal (n = 8), proximal interphalangeal (n = 8), hip (n = 2), knee (n = 2), ankle mortise (n = 2), ankle tarsus (n = 2), metatarsophalangeal (n = 10), interphalangeal of great toe (n = 2), and proximal/distal interphalangeal of the toes (n = 8). ‡ The 66 joints to be examined for swelling are the same as those examined for tenderness, except the hip joints are not included.

Appendix 7: Diagnostic criteria: rheumatoid arthritis

1987 Criteria for the Classification of Acute Arthritis of Rheumatoid Arthritis

Criterion	Definition
1. Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement
2. Arthritis of 3 or more joint areas	At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints
3. Arthritis of hand joints	At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint
4. Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)
5. Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician
6. Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid 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 bony decalcification localised in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)

* For classification purposes, a patient shall be said to have rheumatoid arthritis if he/she has satisfied at least 4 or these 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded. Designation as classic, definite, or probable rheumatoid arthritis is *not* to be made.

Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315---24.

Appendix 8: Health assessment questionnaire (HAQ)

In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

Please tick the response which best describes your usual abilities OVER THE PAST WEEK

	(0) Without ANY Difficulty	(1) With SOME Difficulty	(2) With MUCH Difficulty	(3) UNABLE To Do
1. DRESSING & GROOMING				
Are you able to :				
Dress yourself, including tying shoelaces and doing buttons?	_____	_____	_____	_____
Shampoo your hair?	_____	_____	_____	_____
2. ARISING				
Are you able to :				
Stand up from a straight chair?	_____	_____	_____	_____
-Get in & out of bed?	_____	_____	_____	_____
3. EATING				
Are you able to:				
Cut your meat?	_____	_____	_____	_____
Lift a full cup or glass to your mouth?	_____	_____	_____	_____
-Open a new milk carton?	_____	_____	_____	_____
4. WALKING				
Are you able to :				
Walk outdoors on flat ground?	_____	_____	_____	_____
Climb up five steps?	_____	_____	_____	_____

Please tick **any AIDS OR DEVICES** that you usually use for any of these activities:

Devices used for dressing _____
(button hook, zipper pull, long-handled shoe horn etc)
Built up or special utensils _____
Special or built up chair _____
Other (specify) _____

Walker _____
Crutches _____
Wheelchair _____
Cane _____

Please tick any categories for which you usually need **HELP FROM ANOTHER PERSON.**

Dressing & Grooming_____ Eating _____

Arising _____ Walking _____

Please tick the response which best describes your usual abilities **OVER THE PAST WEEK**

	(0) Without ANY Difficulty	(1) With SOME Difficulty	(2) With MUCH Difficulty	(3) UNABLE To Do
5. HYGIENE				
Are you able to:				
Wash & dry your body?	_____	_____	_____	_____
Take a bath?	_____	_____	_____	_____
Get on & off the toilet?	_____	_____	_____	_____
6. REACH				
Are you able to :				
Reach & get down a 5 pound object (such as a bag of sugar) from just above your head?	_____	_____	_____	_____
Bend down to pick up clothing from the floor?	_____	_____	_____	_____
7. GRIP				
Are you able to :				
Open car doors?	_____	_____	_____	_____
Open jars which have been previously opened?	_____	_____	_____	_____
turn taps on & off?	_____	_____	_____	_____
8. ACTIVITIES				
Are you able to :				
Run errands & shop?	_____	_____	_____	_____
Get in & out of a car?	_____	_____	_____	_____
Do chores such as vacuming or yardwork?	_____	_____	_____	_____

Please tick any **AIDS or DEVICES** that you usually use for any of these activities:

Raised toilet seat _____
Bathtub seat _____
Bathtub bar _____
Other (specify) _____

Long-handled applicances in bathroom _____
Long-handled applicances for reach _____
Jar opener (for jars previously opened) _____

Please tick any caterogies for which you usually need **HELP FROM ANOTHER PERSON**

Hygiene _____
Reach _____
Gripping & opening things _____
Errands & Chores _____

Thank You for Completing this Questionnaire

Appendix 9: Homunculus image permission (Figure 4:2)

---------- Forwarded message ----------
From: Patricia Minnock <minnockp@tcd.ie>
Date: 12 January 2011 18:16
Subject: Re: Permission to use
To: P.vanRiel@reuma.umcn.nl

Dear Prof vanRiel
Many thanks.
Patricia

On 10 January 2011 19:30, <P.vanRiel@reuma.umcn.nl> wrote:
> Dear Patricia,
> No problem!
> Succes with your thesis!
> Kind regards
> Piet
>
> (verzonden vanaf mijn BlackBerry)
> Prof Dr Piet L.C.M. van Riel
> Head Department of Rheumatology
> Radboud University Nijmegen Medical Centre
> http://www.umcn.nl/rheumatology
>
>
> ----- Oorspronkelijk bericht -----
> Van: Patricia Minnock <minnockp@tcd.ie>
> Aan: Riel, Piet van
> Verzonden: Mon Jan 10 20:18:57 2011
> Onderwerp: Permission to use
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> het handelsregister onder nummer 41055629.
> The Radboud University Nijmegen Medical Centre is listed in the
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41055629.
>
>> Dear Prof van Riel
>
> I wish to request your permission to reprint a figure from your
> website in my ongoing Phd project and related publiations- on the
> topic of fatigue in patients with inflammatory arthritis.
>
> I am a final year PhD student at the School of Nursing and Midwifery,
> Trinty College Dublin, Ireland. The figure I require is the 28-joint
> homonculus image on view on the
> http://www.das-score.nl/www.das-score.nl/ website.
>
> I look forward to hearing from you.
>>
> With thanks
> Yours sincerely
> Patricia Minnock, MSc
> Advanced Nurse Practitioner, (Rheumatology) Our Lady's Hospice and
> Care Service and St Vincents University Hospital, Dublin

Appendix 10: Proforma for patient reported outcome measures

This form includes information not available from blood tests, x-rays, or any source other than **YOU**. Please try to answer each question exactly as you think you feel.

For each of the questions indicate how you have been feeling DURING THE PAST WEEK

1. Early Morning Stiffness

How long does your stiffness last for in the morning?

OR

Duration in hours	Duration in minutes

2. How much PAIN have you had….. OVER THE PAST WEEK?

Circle the number that most closely indicates how much pain you had over the last week

1 2 3 4 5 6 7 8 9 10

None at all A great deal

3. Considering all the ways your arthritis affects you….

Circle the number that most closely indicates how active your arthritis has been over the last week

1 2 3 4 5 6 7 8 9 10

Not at all A great deal

4. FATIGUE severity …….OVER THE PAST WEEK?

Please indicate your level of fatigue by choosing the word that closely matches your fatigue

None Mild Moderate Severe Very Severe

Appendix 11: Multidimensional assessment of fatigue (MAF) scale

<u>Instructions</u>: These questions are about fatigue and the effect of fatigue on your activities.

For each of the following questions, circle the number that most closely indicates how you have been feeling during the past week.

For example, suppose you really like to sleep late in the mornings. You would probably circle the number closer to the "a great deal" end of the line. This is where I put it:

Example: To what degree do you usually like to sleep late in the mornings?

1	2	3	4	5	6	7	(8)	9	10

Not at all A great deal

Now please complete the following items based on <u>the past week</u>.

---

1. To what degree have you experienced fatigue?

1	2	3	4	5	6	7	8	9	10

Not at all A great deal

If no fatigue, stop here.

2. How severe is the fatigue which you have been experiencing?

1	2	3	4	5	6	7	8	9	10

Mild Severe

3. To what degree has fatigue caused you distress?

1	2	3	4	5	6	7	8	9	10

No distress A great deal of distress

MULTIDIMENSIONAL ASSESSMENT OF FATIGUE (MAF) SCALE (Continued)

Circle the number that most closely indicates to what degree fatigue has interfered with your ability to do the following activities in the past week. For activities you don't do, for reasons other than fatigue (e.g. you don't work because you are retired), check the box.

In the past week, to what degree has fatigue interfered with your ability to:

(NOTE: Check box to the left of each number if you don't do activity)

☐ **4. Do household chores**

1 2 3 4 5 6 7 8 9 10

Not at all A great deal

☐ **5. Cook**

1 2 3 4 5 6 7 8 9 10

Not at all A great deal

☐ **6. Bathe or wash**

1 2 3 4 5 6 7 8 9 10

Not at all A great deal

☐ **7. Dress**

1 2 3 4 5 6 7 8 9 10

Not at all A great deal

☐ **8. Work**

1 2 3 4 5 6 7 8 9 10

Not at all A great deal

9. Visit or socialize with friends or family

1 2 3 4 5 6 7 8 9 10

Not at all A great deal

MULTIDIMENSIONAL ASSESSMENT OF FATIGUE (MAF) SCALE (Continued)

(NOTE: Check box to the left of each number if you don't do activity)

☐ **10. Engage in sexual activity**

1 2 3 4 5 6 7 8 9 10

Not at all A great deal

☐ **11. Engage in leisure and recreational activities**

1 2 3 4 5 6 7 8 9 10

Not at all A great deal

☐ **12. Shop and do errands**

1 2 3 4 5 6 7 8 9 10

Not at all A great deal

☐ **13. Walk**

1 2 3 4 5 6 7 8 9 10

Not at all A great deal

☐ **14. Exercise, other than walking**

1 2 3 4 5 6 7 8 9 10

Not at all A great deal

15. Over the past week, how often have you been fatigued?

4 Every day

3 Most, but not all days

2 Occasionally, but not most days

1 Hardly any days

16. To what degree has your fatigue changed during the past week?

4 Increased

3 Fatigue has gone up and down

2 Stayed the same

1 Decreased

Thank You for Completing This Questionnaire

Appendix 12: Permission to use multidimensional assessment of fatigue questionnaire

-----Original Message-----
From: [redacted]
Sent: 08 December 2004 19:26
To: Patricia Minnock
Subject: Permission Form to Use the MAF (fwd)

Thank you for your interest.

Username: MAF
Password: xxxxxxx

Basia Belza, PhD, RN
University of Washington
Box 357266, Seattle, WA 98195-7266
VM 206-685-2266 FAX 206-543-4771
Website: http://www.son.washington.edu/

---------- Forwarded message ----------
Date: Wed, 08 Dec 2004 16:59:50 GMT
From: The MAF Web site <basiab@u.washington.edu>
To: Basia Belza <basiab@u.washington.edu>
Subject: Permission Form to Use the MAF

Name: Patricia Minnock
Address: Rheumatology Rehabilitation
Our Lady's Hospice, Harold's Cross, Dublin 6w, Ireland
Phone Number: 003531 406 88741
FAX: 00353 1972 4013
Email: pminnock@olh.ie

Reason for Wanting to Use

Abstract: I am currently preparing a PhD proposal in the area of fatigue and pain in early and established RA.
Timeline for data collection and analysis: Data collection 2005-2006
Data Analysis 2006-2007
Funding: Preparing portfolio and application for submission to the Health Research Board in Ireland.

I will not give out the password to anyone else.
I will use MAF only for my personal research and evaluation.
I will not market or disseminate these measures to others.
I will give Dr. Belza a copy of any research report that uses the MAF.

I agree to all of the above statements.

From: Basia Belza [mailto:basiab@u.washington.edu]

Appendix 13: Letter of introduction to study participants

Dear Sir/Madam,

My name is Patricia Minnock; I am an Advanced Nurse Practitioner in Rheumatology Nursing and am currently a part-time post graduate student undertaking a PhD in the School of Nursing and Midwifery, Trinity College, Dublin. I am writing to you requesting your participation in a study that I am conducting into fatigue in patients with inflammatory arthritis. My supervisors are Prof Cecily Begley, University of Dublin, Trinity College and Prof [redacted] University Hospital, [redacted]. The Health Research Board funds the study.

The current title of this work is - *Fatigue in inflammatory rheumatic diseases: Identifying contributory factors, patients' perceptions of fatigue and potential self-management interventions.*

Patients with inflammatory rheumatic diseases have identified fatigue (often overwhelming and disabling), as an important symptom for which specific treatment is seldom advised or available. Patients, doctors, nurses and researchers have agreed that fatigue assessment would aid understanding and so treatment and management of this major symptom of arthritis.

The aim of the study is examine fatigue in patients with inflammatory rheumatic diseases and to explore patients' perceptions and experiences of fatigue in order to identify potential self-management interventions.

All patients who have been recently prescribed TNFi or biologic therapy medication for their inflammatory arthritis are being invited to take part in this study. We wish to monitor how fatigue behaves in patients prescribed one of these treatments.

If you agree to participate, you will be requested to give the blood samples which are routinely taken to monitor your arthritis and how it responds to treatment and you will also be asked to complete a series of questionnaires before you start your new medication. When you attend the special biologic therapy review clinic in the [redacted] University Hospital 3 months and 6 months after starting your medication these blood tests and questionnaires will be repeated again.

Six months after starting treatment patients who still report fatigue as a major symptom will be asked to complete some additional questionnaires on pain, sleep, mood and self-management skills. Some patients will also be asked to volunteer for interview to explore with me further their own perceptions and personal experiences of fatigue and what patients do to manage their own fatigue.

I have sought and obtained ethical approval from: The Faculty of Health Sciences Ethics Committee; Trinity College Dublin, and [redacted] Hospital Ethics and Medical Research Committee.

There are no perceived additional risks associated with this study. You will not benefit directly from taking part in this study but the information we will obtain will provide further knowledge of this condition. Your identity will remain confidential. A study number will identify you. Your name will not be published or disclosed to anyone outside the study group. Any paperwork will be retained within a secure unit within a locked office which is only accessed by authorised people.

There is no funding available to pay participants in this study. It is not anticipated that you will incur any expenses as a result of participating in this research. However if any travel costs are incurred, these will be covered.

If you have any further questions or concerns about this study you can call the rheumatology department at [redacted] and speak to Patricia Minnock.

Thanking you in anticipation.
Yours sincerely

_____
Patricia Minnock
Advanced Nurse Practitioner (Rheumatology)
RGN, RM, FFNRCSI, Dip N, BSc, (Hons), MSc.

Appendix 14: Patient information leaflets and consent form(s)

Phase 1 Part 1

PARTICIPANT INFORMATION AND CONSENT FORM

You are being invited to participate in a research study. Thank you for taking time to read this information.

STUDY TITLE: ***A mixed methods study to determine contributing factors and patients perceptions of fatigue in inflammatory arthritis***

NAME OF PRINCIPAL INVESTIGATOR:

Patricia Minnock, Advanced Nurse Practitioner (Rheumatology)

WHAT IS THE PURPOSE OF THIS STUDY?

The aim of the study is examine fatigue in patients with inflammatory rheumatic diseases and to explore patients' perceptions and experiences of fatigue in order to identify potential self-management interventions.

WHY HAVE I BEEN CHOSEN?

You have been chosen because you have been recently prescribed **TNFi or biologic therapy** medication to treat your inflammatory arthritis. We wish to monitor how fatigue behaves in patients with arthritis that requires treatment with one of these biologic treatments.

WHAT WILL HAPPEN IF I VOLUNTEER?

Your participation is entirely voluntary. If you initially decide to take part you can subsequently change your mind without difficulty. This will not affect your future treatment in any way. Furthermore your doctor may decide to withdraw you from this study if he/she feels it is in your best interest.

Part 1

If you agree to participate, in the first phase of the study, you will be requested to give the blood samples which are routinely taken to monitor your arthritis and how it responds to treatment and you will also be asked to complete a series of questionnaires before you start your new medication. When you attend the special biologic therapy review clinic in the [redacted] 3 months and 6 months after starting your medication these blood tests and questionnaires will be repeated again.

Part 2

For the second phase of the study, you may be asked to complete some additional questionnaires on pain, sleep, mood and self-management skills.

During the study additional information relating to your arthritis may be taken from your hospital chart and x-rays.

ARE THERE ANY BENEFITS FROM MY PARTICIPATION?

You will not benefit directly from taking part in this study but the information we will obtain will provide further knowledge of this condition.

ARE THERE ANY RISKS INVOLVED IN PARTICIPATING?

There are no perceived additional risks associated with this study. Should completing the additional questionnaires at six months raise any issues or cause you distress, appropriate support and counselling will be available to you.

WHAT HAPPENS IF I DO NOT AGREE TO PARTICIPATE?

If you decide not to participate in this study your treatment will not be affected in any way.

CONFIDENTIALITY

Your identity will remain confidential. A study number will identify you. Your name will not be published or disclosed to anyone outside the study group. Any paperwork will be retained within a secure unit within a locked office which is only accessed by authorised people.

COMPENSATION

Your doctors are adequately insured by virtue of their participation in the clinical indemnity scheme. Nothing in this document restricts or curtails your rights.

WHO IS ORGANISING AND FUNDING THIS RESEARCH?

This study is organised by Patricia Minnock, Advanced Nurse Practitioner (Rheumatology) under the supervision of Prof Cecily Begley, University of Dublin, Trinity College and Prof [redacted] The Health Research Board funds the study.

Will I be paid for taking part in this study?

There is no funding available to pay participants in this study. You have volunteered to participate in this study. You may withdraw at any time. If you decide not to participate, or if you withdraw, you will not be penalised and will not give up any benefits that you had before entering the study.

Will my expenses be covered for taking part in this study?

It is not anticipated that you will incur any expenses as a result of participating in this research. However if any travel costs are incurred, these will be covered.

IS THIS STUDY SAFE AND BENEFICIAL?

The [redacted] Healthcare Group, Ethics and Medical Research Committee and the Research Ethics Committee, Faculty of Health Sciences, Trinity College Dublin, have reviewed and approved this study.

The investigators may withdraw your participation in the study at any time without your consent.

CONTACT DETAILS

If you have any further questions or concerns about this study, your participation in the study, and your rights, you can call the rheumatology department at [redacted] and speak to Patricia Minnock.

(Phase 1 Part 2)

PARTICIPANT INFORMATION AND CONSENT FORM

STUDY TITLE: ***A mixed methods study to determine contributing factors and patients perceptions of fatigue in inflammatory arthritis***

NAME OF PRINCIPAL INVESTIGATOR:
Patricia Minnock, Advanced Nurse Practitioner (Rheumatology)

Thank you for taking the time, IN THE PAST, to take part in this study of fatigue in patients with inflammatory arthritis prescribed TNFi or biologic therapy medication.

You are now being invited to contribute further in this research study by completing some additional questionnaires.

WHY HAVE I BEEN CHOSEN?
You have been chosen because you agreed to participate in an earlier phase of this study during your first year of your **biologic therapy** medication.

HOW CAN I CONTRIBUTE NOW?
Please take time to complete the enclosed questionnaires on pain, sleep, mood and self-management skills of patients and return them to me in the freepost addressed envelope supplied.

CONTACT DETAILS
If you have any further questions or concerns about this study, your participation in the study, and your rights, you can call the rheumatology department at [redacted] and speak to Patricia Minnock.

PARTICIPANT INFORMATION AND CONSENT FORM

(Phase 2)

STUDY TITLE: ***A mixed methods study to determine contributing factors and patients perceptions of fatigue in inflammatory arthritis***

NAME OF PRINCIPAL INVESTIGATOR:

Patricia Minnock, Advanced Nurse Practitioner (Rheumatology)

You are being invited to participate in a research study. Thank you for taking time to read this.

WHAT IS THE PURPOSE OF THIS STUDY?

The aim of the study is examine fatigue in patients with inflammatory rheumatic diseases and to explore patients' perceptions and experiences of fatigue in order to identify potential self-management interventions.

WHY HAVE I BEEN CHOSEN?

You have been chosen because you participated in an earlier phase of this study and we now wish to further explore, through interview, patients own perceptions and personal experiences of fatigue and what patients do to manage their own fatigue.

WHAT WILL HAPPEN IF I VOLUNTEER?

Your participation is entirely voluntary. If you initially decide to take part you can subsequently change your mind without difficulty. This will not affect your future treatment in any way. Furthermore your doctor may decide to withdraw you from this study if he/she feels it is in your best interest.

If you agree to participate, you will be requested to attend an interview to talk about your experience of fatigue. The length of the interview will be approximately 1 to 1 and 1/2 hours but this may vary depending on the information shared. If you require a break at any stage in the interview, or if you wish to resume the interview on another day, this can be organised.

ARE THERE ANY BENEFITS FROM MY PARTICIPATION?

You will not benefit directly from taking part in this study although research interviews can sometimes have therapeutic effects. The interview can sometimes be an enriching experience enabling you to gain new insights into your life situation.

ARE THERE ANY RISKS INVOLVED IN PARTICIPATING?

There are no perceived additional risks associated with this study. Should any issues raised cause you distress, appropriate support and counselling will be available to you.

WHAT HAPPENS IF I DO NOT AGREE TO PARTICIPATE?

If you decide not to participate in this study your treatment will not be affected in any way.

CONFIDENTIALITY

Your identity will remain confidential. A study number will identify you. Your name will not be published or disclosed to anyone. Any paperwork will be retained within a secure unit within a locked office, which is only accessed by authorised people.

COMPENSATION

Your doctors are adequately insured by virtue of their participation in the clinical indemnity scheme.

WHO IS ORGANISING AND FUNDING THIS RESEARCH?

This study is organised by Patricia Minnock, Advanced Nurse Practitioner (Rheumatology) under the supervision of Prof Cecily Begley, University of Dublin, Trinity College and Prof [redacted] The Health Research Board funds the study.

Will I be paid for taking part in this study?

There is no funding available to pay participants in this study.

Will my expenses be covered for taking part in this study?

It is not anticipated that you will incur any expenses as a result of participating in this research. However if any travel costs are incurred, these will be covered.

IS THIS STUDY SAFE AND BENEFICIAL?

The [redacted] Healthcare Group, Ethics and Medical Research Committee have reviewed and approved this study.

CONTACT DETAILS

If you have any further questions or concerns about this study you can call the rheumatology department [redacted] and speak to Patricia Minnock.

CONSENT

STUDY TITLE: ***A mixed methods study to determine contributing factors and patients perceptions of fatigue in inflammatory arthritis***

NAME OF PRINCIPAL INVESTIGATOR:

Patricia Minnock, Advanced Nurse Practitioner (Rheumatology)

The Participant must complete this section himself/herself.

PLEASE TICK YOUR RESPONSE IN THE APPROPRIATE BOX

I have read and understood the attached Participant Information	YES □ NO □
I have had the opportunity to ask questions and discuss the study	YES □ NO □
I have received satisfactory answers to all my questions	YES □ NO □
I have received enough information about this study	YES □ NO □
I understand that I am free to withdraw from the study at any time without giving a reason and without this affecting my future medical care	YES □ NO □
I agree to take part in the study	**YES □ NO □**

Participant's Signature: _____ Date: _____

Participant's Name in print: _____

Witness Signature: _____ Date: _____

Witness Name in print: _____

I have explained the nature and purpose of this research study, the procedures to be undertaken and any risks that may be involved. I have offered to answer any questions and fully answered such questions. I believe that the participant understands my explanation and has freely given informed consent.

Investigator's Signature: _____ Date: _____

Investigator's Name in print: _____

Appendix 15: Exploratory data analysis

Testing for Normality of Data Distribution

The fatigue and core set variables were tested for normality of distribution of the data using the Shapiro-Wilk test. If the significance value of the Shapiro-Wilk Test is greater the 0.05 then the data are normal. If it is below 0.05 then the data significantly deviate from a normal distribution. All variables deviate from a normal distribution with the exception of DAS28 at baseline. Therefore mean and median values and parametric and non-parametric test were employed as appropriate.

Baseline Data

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
MAF_0	.107	116	.002	.962	116	.002
HAQ_0	.081	116	.062	.965	116	.004
SJC28_0	.129	116	.000	.924	116	.000
TJC28_0	.144	116	.000	.913	116	.000
Pain_0	.139	116	.000	.959	116	.001
GH_0	.161	116	.000	.959	116	.001
CRP_0	.255	116	.000	.694	116	.000
DAS28_0	.045	116	.200*	.993	116	.850

a. Lilliefors Significance Correction

*. This is a lower bound of the true significance.

3-Month Data

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
MAF_3	.110	84	.014	.946	84	.002
SJC28_3	.235	84	.000	.748	84	.000
TJC28_3	.260	84	.000	.672	84	.000
Pain_3	.216	84	.000	.915	84	.000
GH_3	.178	84	.000	.934	84	.000
HAQ_3	.142	84	.000	.891	84	.000
CRP_3	.242	84	.000	.571	84	.000
DAS28_3	.086	84	.186	.958	84	.008

a. Lilliefors Significance Correction

6-Month Data

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
SJC28_6	.276	75	.000	.694	75	.000
TJC28_6	.295	75	.000	.584	75	.000
Pain_6	.154	75	.000	.917	75	.000
GH_6	.167	75	.000	.923	75	.000
MAF_6	.066	75	.200*	.972	75	.090
HAQ_6	.135	75	.002	.909	75	.000
CRP_6	.356	75	.000	.374	75	.000
DAS28_6	.142	75	.001	.913	75	.000

a. Lilliefors Significance Correction

*. This is a lower bound of the true significance.

Haemoglobin and Early Morning Stiffness Data at Baseline, 3 and 6-Months

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
HB.0gperdl	.108	21	.200*	.976	21	.851
HB.3gperdl	.094	21	.200*	.966	21	.639
HB.6gperdl	.152	21	.200*	.928	21	.125
Stiffness.0Minutes	.337	21	.000	.474	21	.000
Stiffness.3minutes	.480	21	.000	.267	21	.000
Stiffness.6minutes	.206	21	.021	.803	21	.001

a. Lilliefors Significance Correction

*. This is a lower bound of the true significance.

Within Groups one Way Analysis of Variance (ANOVA)

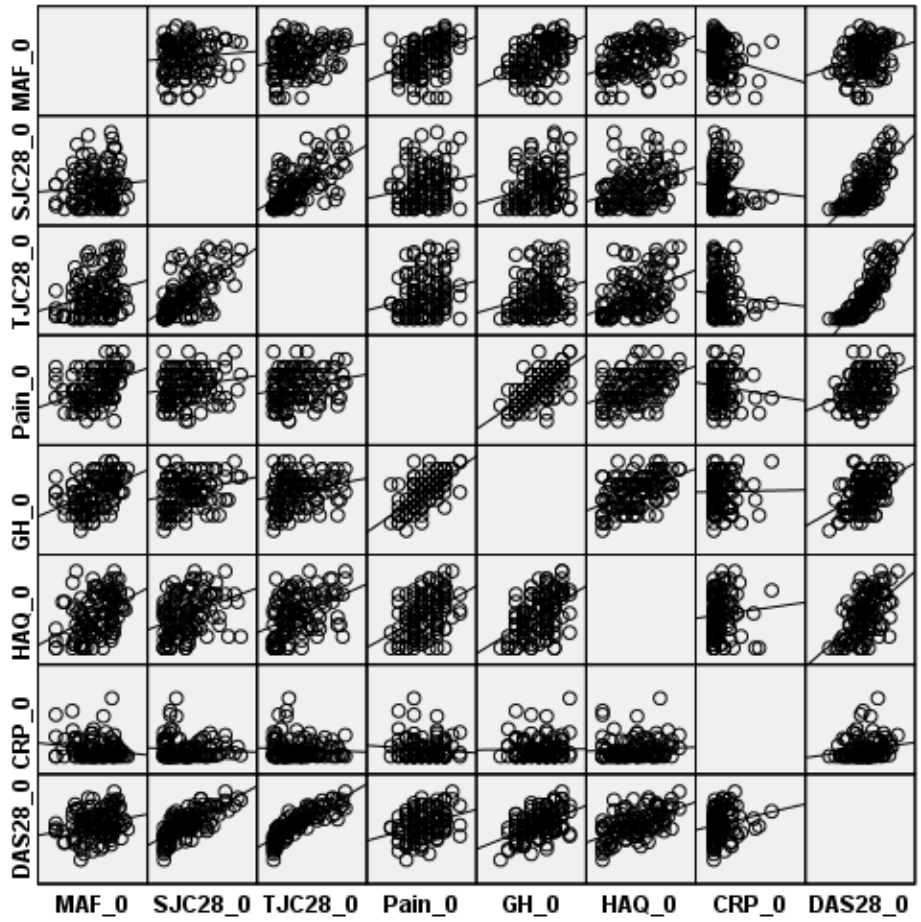
Within groups one-way ANOVA, which examines the difference between means of more than two treatment groups, was used to test the null hypothesis of equal treatment means between the clinical variables (core set outcomes and fatigue) at the 3 separate time points. Model Assumptions include:

1. Normal distribution
2. Equal within group variance
3. Spehericity – homogeneity of covariance (equal paired group variances)

Although the data for the core set variable and the multidimensional fatigue scales (MAF) were not normally distributed the parametric test ANOVA was used as it is generally held that ANOVA is <u>not</u> greatly influenced if the distribution is not normal as long as scores are symmetrically distributed, sample sizes equal and are greater than 12. Variances can differ by a factor of four without type 1 or type 2 error rates rising unacceptably (Keppel and Wickens 2004; Howell 2007). The non-parametric equivalent tests (Kruskal-Wallis) involve an initial process of converting scalar data set to ranks with associated risks of loss of power for this reason the robust parametric ANOVA is advocated in preference (Kinnear and Gray 2009) p266.

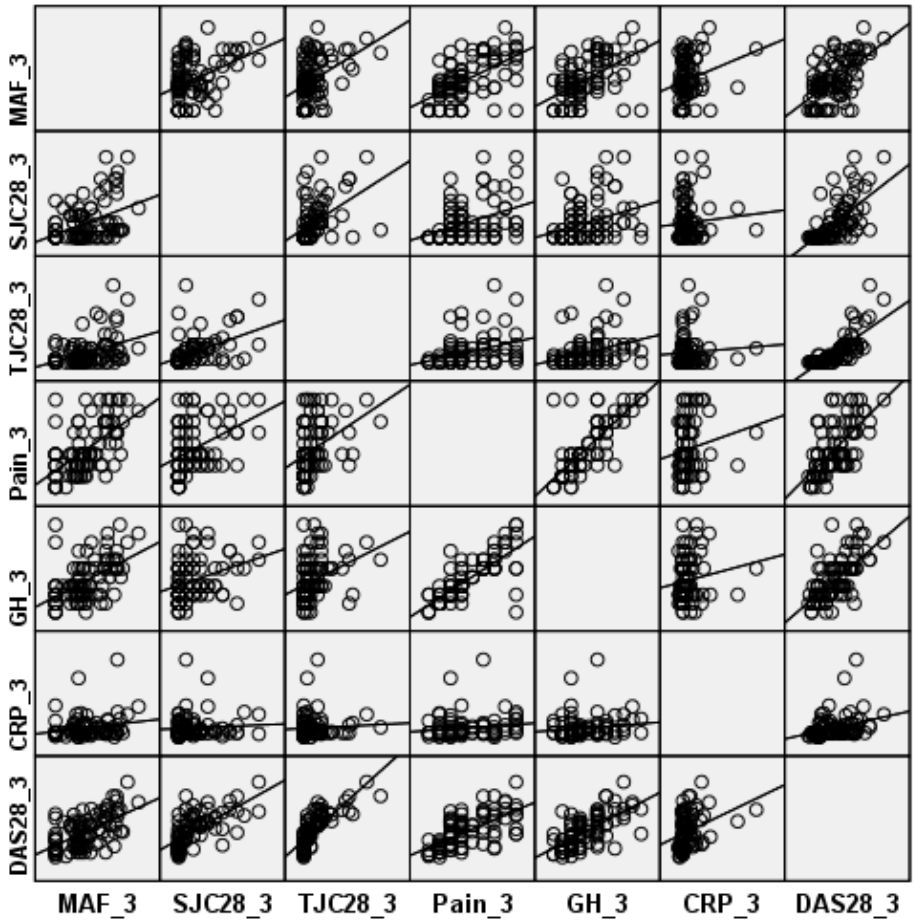
Correlation Matrix: Examination of Linear Relationship between Fatigue and Core Set Variables at Baseline

Observation of the correlation matrix detects linear, non-linear and monotonic relationships between variables at baseline, 3-months and 6-months.



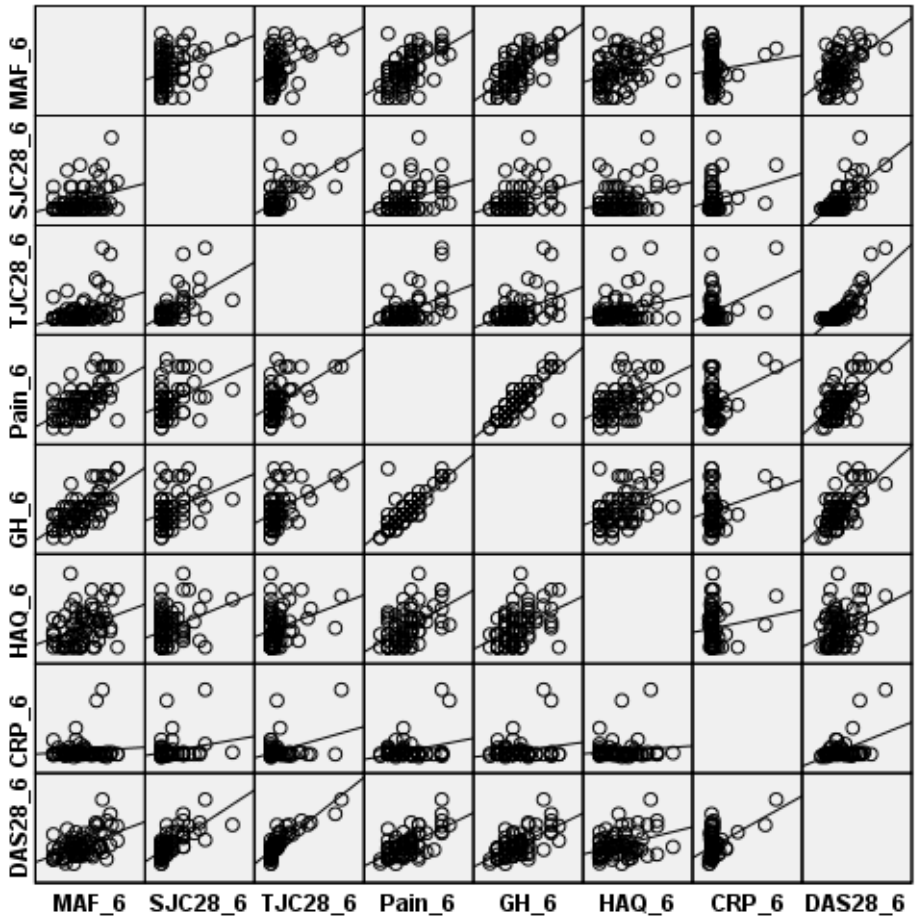
MAF_0: Multidimensional Assessment of Fatigue Scale- Global Fatigue Index at baseline; SJC28_0: Swollen Joint Count 28 at baseline; TJC28_0: Tender Joint Count 28 at baseline; Pain_0 VAS: Pain visual analogue scale at baseline; GH_0: Patient Global Health at baseline; HAQ_0: Health Assessment Questionnaire at baseline; CRP_0: C-reactive protein at baseline; DAS28_0: Disease Activity Score 4-variable CRP at baseline;

Correlation Matrix: Examination of Linear Relationship between Fatigue and Core Set Variables at 3-Months



MAF_3: Multidimensional Assessment of Fatigue Scale- Global Fatigue Index at 3-months; SJC28_3: Swollen Joint Count 28 at 3-months; TJC28_3: Tender Joint Count 28 at 3-months; Pain_3 VAS: Pain visual analogue scale at 3-months; GH_3: Patient Global Health at 3-months; HAQ_3: Health Assessment Questionnaire at 3-months; CRP_3: C-reactive protein at 3-months; DAS28_3: Disease Activity Score 4-variable CRP at 3-months.

Correlation Matrix: Examination of Linear Relationship between Fatigue and Core Set Variables at 6-Months



MAF_6: Multidimensional Assessment of Fatigue Scale- Global Fatigue Index at 6-months; SJC28_6: Swollen Joint Count 28 at 6-months; TJC28_6: Tender Joint Count 28 at 6-months; Pain_6 VAS: Pain visual analogue scale at 6-months; GH_6: Patient Global Health at 6-months; HAQ_6: Health Assessment Questionnaire at 6-months; CRP_6: C-reactive protein at 6-months; DAS28_6: Disease Activity Score 4-variable CRP at 6-months.

Exploratory Factor Analysis: Stage 1

Inspection of the R-matrix shows an association between all variables, with the exception of CRP, which are equal or greater than the minimum recommended correlation of 0.3 for full factor analysis.

Exploratory factor analysis: matrix of correlation coefficients at baseline

Correlation Matrix

		MAF_0	SJC28_0	TJC28_0	Pain_0	GH_0	HAQ_0	CRP_0
Correlation	MAF_0	1.000	.092	.240	.383	.443	.430	-.182
	SJC28_0	.092	1.000	.628	.183	.241	.346	-.069
	TJC28_0	.240	.628	1.000	.218	.237	.428	-.072
	Pain_0	.383	.183	.218	1.000	.686	.439	-.107
	GH_0	.443	.241	.237	.686	1.000	.486	.013
	HAQ_0	.430	.346	.428	.439	.486	1.000	.072
	CRP_0	-.182	-.069	-.072	-.107	.013	.072	1.000

Exploratory factor analysis: matrix of correlation coefficients at 3-months

Correlation Matrix

		MAF_3	SJC28_3	TJC28_3	Pain_3	GH_3	HAQ_3	CRP_3
Correlation	MAF_3	1.000	.418	.433	.575	.500	.334	.190
	SJC28_3	.418	1.000	.463	.387	.289	.375	.054
	TJC28_3	.433	.463	1.000	.381	.343	.213	.060
	Pain_3	.575	.387	.381	1.000	.761	.461	.108
	GH_3	.500	.289	.343	.761	1.000	.376	.078
	HAQ_3	.334	.375	.213	.461	.376	1.000	.032
	CRP_3	.190	.054	.060	.108	.078	.032	1.000

Exploratory factor analysis: matrix of correlation coefficients at 6-months

Correlation Matrix

		MAF_6	SJC28_6	TJC28_6	Pain_6	GH_6	HAQ_6	CRP_6
Correlation	MAF_6	1.000	.326	.390	.575	.686	.360	.102
	SJC28_6	.326	1.000	.592	.370	.354	.319	.232
	TJC28_6	.390	.592	1.000	.499	.463	.291	.368
	Pain_6	.575	.370	.499	1.000	.831	.529	.310
	GH_6	.686	.354	.463	.831	1.000	.452	.217
	HAQ_6	.360	.319	.291	.529	.452	1.000	.121
	CRP_6	.102	.232	.368	.310	.217	.121	1.000

Correlation matrices confirmed the linear relationship between fatigue and all variables at each of the three time points. The collinearity between pain and global health was r=0.72 at baseline; r=0.73 at 3-months; and r=0.84 at 6-months. All others were less than the recommended value of r >0.7 (Kerr *et al.* 2002). Following exploratory analysis a decision was made not to exclude any variable from the analysis as the model fit according to ANOVA (ratio of sum of squares regression to sum of squares residuals) was best when all

variables were included. As part of the regression procedure on SPSS (SPSS.com 2009) casewise diagnostics were run to confirm the absence of outliers within the respective data sets before proceeding with the regression analysis. The normal probability plot for the residuals supported the validity of the analyses. Thus the model assumption of normal distribution of the chance variation was supported at baseline, 3 and 6-months.

Test for Collinearity among Change Variables at 3-months

Correlations

		DeltaMAF0_3	DeltaHAQ0_3	DeltaSJC0_3	DeltaTJC0_3	DeltaPain0_3	DeltaGH0_3	DeltaCRP0_3
DeltaMAF0_3	Pearson Correlation	1	.251*	.084	.183	.358**	.321**	-.069
	Sig. (2-tailed)		.020	.432	.084	.001	.002	.524
	N	95	86	90	90	90	91	87
DeltaHAQ0_3	Pearson Correlation	.251*	1	.231*	.108	.235*	.152	-.005
	Sig. (2-tailed)	.020		.022	.291	.019	.128	.959
	N	86	102	98	98	99	101	95
DeltaSJC0_3	Pearson Correlation	.084	.231*	1	.576**	.091	.039	-.065
	Sig. (2-tailed)	.432	.022		.000	.359	.689	.516
	N	90	98	107	107	103	105	101
DeltaTJC0_3	Pearson Correlation	.183	.108	.576**	1	.114	.129	-.023
	Sig. (2-tailed)	.084	.291	.000		.253	.190	.818
	N	90	98	107	107	103	105	101
DeltaPain0_3	Pearson Correlation	.358**	.235*	.091	.114	1	.584**	-.139
	Sig. (2-tailed)	.001	.019	.359	.253		.000	.170
	N	90	99	103	103	106	106	99
DeltaGH0_3	Pearson Correlation	.321**	.152	.039	.129	.584**	1	-.004
	Sig. (2-tailed)	.002	.128	.689	.190	.000		.965
	N	91	101	105	105	106	108	101
DeltaCRP0_3	Pearson Correlation	-.069	-.005	-.065	-.023	-.139	-.004	1
	Sig. (2-tailed)	.524	.959	.516	.818	.170	.965	
	N	87	95	101	101	99	101	106

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Test for Collinearity among Change Variables at 6-months

Correlations

		DeltaMAF0_6	DeltaHAQ0_6	DeltaSJC0_6	DeltaTJC0_6	DeltaPain0_6	DeltaGH0_6	DeltaCRP0_6
DeltaMAF0_6	Pearson Correlation	1	.146	.001	-.033	.082	.230	-.083
	Sig. (2-tailed)		.317	.995	.815	.562	.094	.548
	N	85	49	53	53	53	54	55
DeltaHAQ0_6	Pearson Correlation	.146	1	.158	-.089	.438**	.345**	-.056
	Sig. (2-tailed)	.317		.177	.445	.000	.002	.630
	N	49	79	75	75	75	77	76
DeltaSJC0_6	Pearson Correlation	.001	.158	1	.516**	.021	.036	-.166
	Sig. (2-tailed)	.995	.177		.000	.853	.750	.142
	N	53	75	82	82	79	81	80
DeltaTJC0_6	Pearson Correlation	-.033	-.089	.516**	1	.064	.118	-.043
	Sig. (2-tailed)	.815	.445	.000		.577	.294	.707
	N	53	75	82	82	79	81	80
DeltaPain0_6	Pearson Correlation	.082	.438**	.021	.064	1	.700**	-.052
	Sig. (2-tailed)	.562	.000	.853	.577		.000	.647
	N	53	75	79	79	83	83	80
DeltaGH0_6	Pearson Correlation	.230	.345**	.036	.118	.700**	1	.033
	Sig. (2-tailed)	.094	.002	.750	.294	.000		.770
	N	54	77	81	81	83	85	82
DeltaCRP0_6	Pearson Correlation	-.083	-.056	-.166	-.043	-.052	.033	1
	Sig. (2-tailed)	.548	.630	.142	.707	.647	.770	
	N	55	76	80	80	80	82	85

**. Correlation is significant at the 0.01 level (2-tailed).

There was no evidence of colinearity between the 0-3 month Δ variables (r values <.584). The colinearity between the 0-6 month Δ variables for pain and global heath was r=0.7, all

others were less than the recommended value of r >0.7 (Kerr *et al.* 2002). All variables were included in the analysis. The normal probability plot for the residuals supported the validity of the analyses.

Diagnostics for Multiple Regression Analysis of Fatigue and Core Set Variables at 3-Months and at 6-Months

The guideline of 50 cases minimum plus eight cases for each variable was taken to support statistical analysis with seven independent variables (Tabachnick and Fidell 2001)

Initial casewise diagnostics showed 2 outliers with absolute standardised residuals > 3. These were case number 4 and number 96. Both case were eliminated as each were missing fatigue (MAF) data at least one time point. When these outliers were eliminated the regression analysis was re-run.

(a) Case wise diagnostics at 3-months

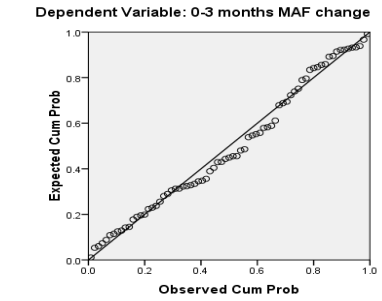
Case Number	Std. Residual	0-3 months MAF change	Predicted Value	Residual
4	3.018	41.00	7.5940	33.40601
96	-3.264	-36.91	-.7822	-36.12690

a. Dependent Variable: 0-3 months MAF change

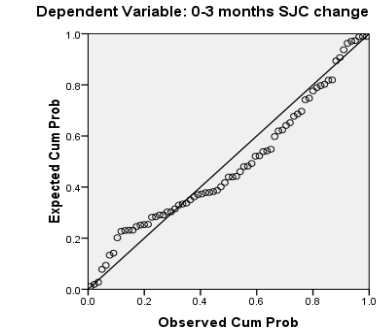
(b) Residuals at 3 months and 6-months

Residuals are the basis of regression diagnostics, that is, procedures for testing that the model assumptions are upheld. The cumulative normal probability plot of the Standardised Residuals (outliers eliminated) show that the points lie on or adjacent to the diagonal which support the model assumptions of linearity and homogeneity of variance of the data (change score in MAF and core set variables at 3-months and at 6-months).

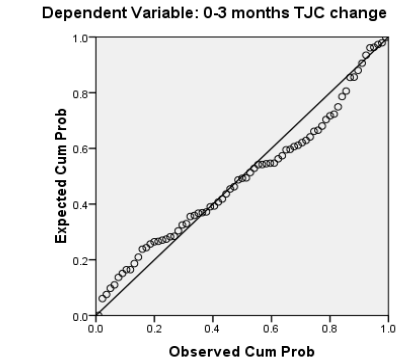
Normal P-P Plot of Regression Standardized Residual



Normal P-P Plot of Regression Standardized Residual

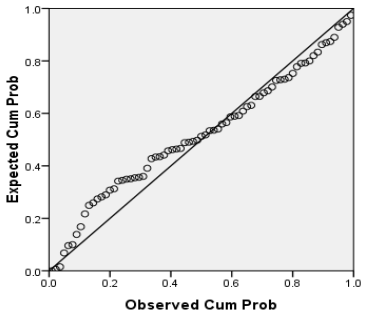


Normal P-P Plot of Regression Standardized Residual



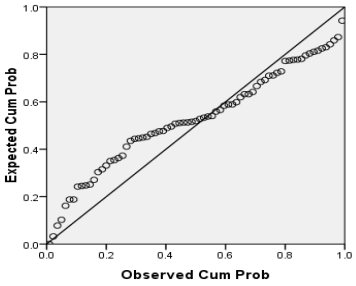
Normal P-P Plot of Regression Standardized Residual

Dependent Variable: 0-3 months Pain change



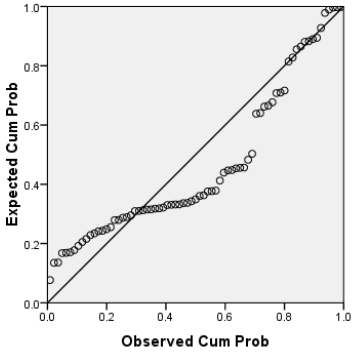
Normal P-P Plot of Regression Standardized Residual

Dependent Variable: 0-3 months HAQ change



Normal P-P Plot of Regression Standardized Residual

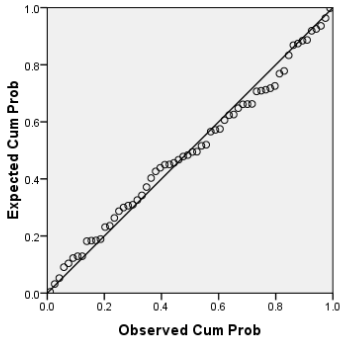
Dependent Variable: 0-3 months CRP change



Multiple Regression Analysis at 6-Months

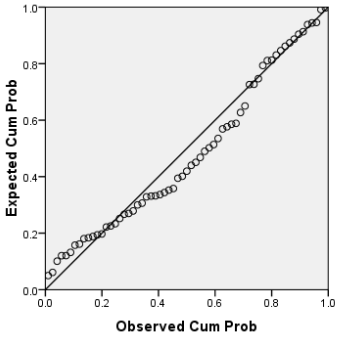
Normal P-P Plot of Regression Standardized Residual

Dependent Variable: 0-6 months MAF change



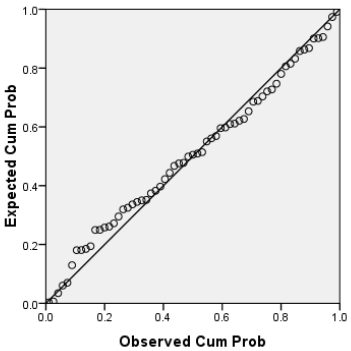
Normal P-P Plot of Regression Standardized Residual

Dependent Variable: 0-6 months SJC change



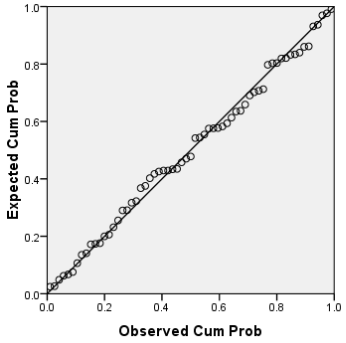
Normal P-P Plot of Regression Standardized Residual

Dependent Variable: 0-6 months Pain change



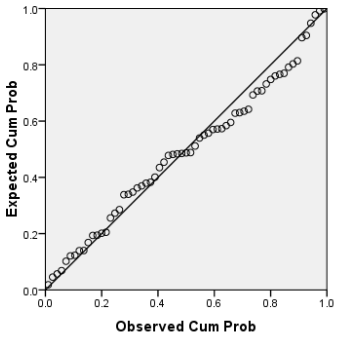
Normal P-P Plot of Regression Standardized Residual

Dependent Variable: 0-6 months GH change



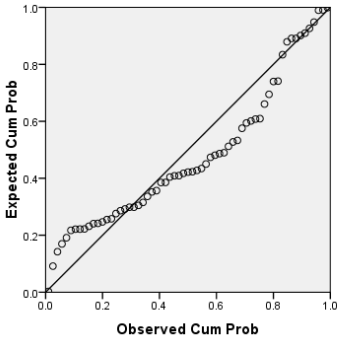
Normal P-P Plot of Regression Standardized Residual

Dependent Variable: 0-6 months HAQ change



Normal P-P Plot of Regression Standardized Residual

Dependent Variable: 0-6 months CRP change



Testing for normality of distribution of data related to poor fatigue outcome and good fatigue outcome subgroups.

All variables (socio-demographic, McGill Pain Questionnaire, Arthritis Self-Efficacy, PSQI, POMS, BDI, BHS) (Kinnear and Gray 2009). ***If it is below 0.05 then the data significantly deviate from a normal distribution.***

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
DAS28CRP.6	.173	30	.022	.909	30	.014
HAQ.6	.136	30	.166	.951	30	.178
HB.6	.107	30	.200*	.974	30	.653
Stiffness.6	.185	30	.010	.866	30	.001

a. Lilliefors Significance Correction

*. This is a lower bound of the true significance.

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
A_MPQ_Descriptor	.206	56	.000	.845	56	.000
B_MPQ_VAS_Rating	.134	56	.014	.911	56	.001
C_MPQ_CPI	.183	56	.000	.883	56	.000
SE_PAIN_MEAN	.068	56	.200*	.976	56	.334
SE_FUNCTIONING_MEAN	.163	56	.001	.905	56	.000
SE_Other_Symptoms_Mean	.101	56	.200*	.951	56	.023
TotalPomsScore	.137	56	.010	.934	56	.004
PSQI_GLOBAL	.146	56	.004	.890	56	.000
BDI_Total	.130	56	.020	.945	56	.013
BHS_Total	.231	56	.000	.824	56	.000

a. Lilliefors Significance Correction

*. This is a lower bound of the true significance.

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
PSQI_Duration	.295	59	.000	.750	59	.000
PSQI_Disturbance	.242	59	.000	.874	59	.000
PSQI_Latency	.215	59	.000	.868	59	.000
PSQI_Daytimedysfunction	.263	59	.000	.851	59	.000
PSQI_HSE	.209	59	.000	.836	59	.000
PSQI_Quality	.228	59	.000	.819	59	.000
PSQI_Medications	.434	59	.000	.578	59	.000
PSQI_GLOBAL	.143	59	.004	.907	59	.000

a. Lilliefors Significance Correction

All variables deviate from a normal distribution with the exception of Self-Efficacy Pain Scale. Therefore non parametric tests were employed for all statistical analysis with the exception of the independent t-test for comparison of two self-efficacy pain variable means.

Appendix 16: Comparison of baseline variables between sample (n=87) with and without (n=43) 6-month assessment data

Baseline Demographic &Clinical Details		**Completed 3-timepoint assessments %**	**Missing 6-month Assessment %**	***p***
Total N = 130 (100%)		**87 (67%)**	**43 (33%)**	
Female gender		76	51†	$p \leq 0.001$
Mean age ± SD		53 ± 12	51 ± 13	NS
(range), years		(26-77)	(23-81)	
Mean disease duration ± SD		12 ± 10	12 ± 11	NS
(range), years		(1-39)	(1-35)	
Rheumatoid Factor	Sero-positive	53	53	NS
Diagnosis	RA	74	62	
	PsA	26	38	
Ever Failed DMARD		61	68	
Ever Failed Biologic Drug		1	4	
Smoking Status:	Current	27	25	
	Previous	37	44	
	Non-smoker	36	30	
Educational Background	Primary	21	23	
	Secondary	39	39	
	Third	39	39	
Median Haemoglobin Levels g/dl		13.0	13.0	
Median Early Morning Stiffness Minutes		30	60	NS
(range)		(0-1440)	(0-1440)	
Mean MAF ± SD		26.7 ± 11.0	28.3 ± 9.9	NS
(range)		(1.0 - 44.9)	(5.3 - 43.5)	
Mean DAS28CRP ± SD		5.0 ± 1.1	5.0 ± 1.2	NS
(range),		(2.66 - 7.91)	(2.92 - 7.26)	

RA rheumatoid arthritis; PsA psoriatic arthritis; MAF Multidimensional assessment of fatigue scale; DAS28 CRP, disease activity score 28 C-reactive protein; † Chi-square test for nominal data.

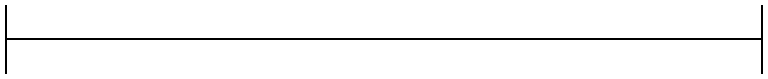
Appendix 17: Short-Form McGill Pain Questionnaire (SF-MPQ)

A. PLEASE DESCRIBE YOUR PAIN DURING THE LAST WEEK. (Check off one box per line.)

	None	Mild	Moderate	Severe
1. Throbbing	0 ☐	1 ☐	2 ☐	3 ☐
2. Shooting	0 ☐	1 ☐	2 ☐	3 ☐
3. Stabbing	0 ☐	1 ☐	2 ☐	3 ☐
4. Sharp	0 ☐	1 ☐	2 ☐	3 ☐
5. Cramping	0 ☐	1 ☐	2 ☐	3 ☐
6. Gnawing	0 ☐	1 ☐	2 ☐	3 ☐
7. Hot-burning	0 ☐	1 ☐	2 ☐	3 ☐
8. Aching	0 ☐	1 ☐	2 ☐	3 ☐
9. Heavy (like a weight)	0 ☐	1 ☐	2 ☐	3 ☐
10. Tender	0 ☐	1 ☐	2 ☐	3 ☐
11. Splitting	0 ☐	1 ☐	2 ☐	3 ☐
12. Tiring-Exhausting	0 ☐	1 ☐	2 ☐	3 ☐
13. Sickening	0 ☐	1 ☐	2 ☐	3 ☐
14. Fear-causing	0 ☐	1 ☐	2 ☐	3 ☐
15. Punishing-Cruel	0 ☐	1 ☐	2 ☐	3 ☐

B. PLEASE RATE YOUR PAIN DURING THE LAST WEEK.

The following line represents pain of increasing intensity from "no pain" to "worst possible pain". Place a vertical mark (|) across the line in the position that best describes your pain **during the last week.**



No Pain — **Worst Possible Pain**

Score in mm *(Investigator's use only)*

C. CURRENT PAIN INTENSITY

0 ☐ No pain
1 ☐ Mild
2 ☐ Discomforting
3 ☐ Distressing
4 ☐ Horrible
5 ☐ Excruciating

Appendix 18: Permission to use the McGill Pain Questionnaire-Short Form

From: Ronald Melzack, Dr. [mailto:ronald.melzack@mcgill.ca]

Sent: 03 February 2011 18:25

To: Patricia Minnock

Subject: RE: Permission to use the short Form Mc Gill pain questionnaire

Dear Patricia,

Thank you for your email.

You have my permission to use the SF-MPQ in your research.

Best wishes.

Ronald Melzack

Appendix 19: Arthritis Self-Efficacy Scales (Lorig And Chastain, 1989)

Self-efficacy pain subscale

In the following questions, we'd like to know how your arthritis pain affects you. For each of the following questions, please circle the number which corresponds to your certainty that you can *now* perform the following tasks:

1. How certain are you that you can decrease your pain *quite a bit*?
2. How certain are you that you can continue most of your daily activities?
3. How certain are you that you can keep arthritis pain from interfering with your sleep?
4. How certain are you that you can make a *small to moderate* reduction in your arthritis pain by using methods other than taking extra medication?
5. How certain are you that you can make a *large* reduction in your arthritis pain by using methods other than taking extra medication?

Self-efficacy function subscale

We would like you to know how confident you are in performing certain daily activities. For each of the following questions, please circle the number which corresponds to your certainty that you can perform the tasks as of *now*, *without* assistive devices or help from another person. Please consider what you *routinely* can do, not what would require a single extraordinary effort.

AS OF NOW, HOW CERTAIN ARE YOU THAT YOU CAN

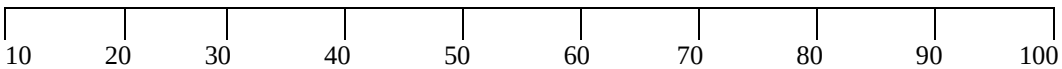
1. Walk 100 feet on flat ground in 20 seconds?
2. Walk 10 steps downstairs in 7 seconds?
3. Get out of armless chair quickly, without using your hands for support?
4. Button and unbutton 3 medium-size buttons in a row in 12 seconds?
5. Cut 2 bite-size pieces of meat with a knife and fork in 8 seconds?
6. Turn an outdoor faucet all the way on and all the way off?
7. Scratch your upper back with both your right and left hands?
8. Get in and out of the passenger side of a car without assistance from another person and without physical aids?
9. Put on a long-sleeve front-opening shirt or blouse (without buttoning) in 8 seconds?

Self-efficacy other symptoms subscale

In the following questions, we'd like to know how you feel about your ability to control your arthritis. For each of the following questions, please circle the number which corresponds to the certainty that you can *now* perform the following activities or tasks.

1. How certain are you that you can control your fatigue?
2. How certain are you that you can regulate your activity so as to be active without aggravating your arthritis?
3. How certain are you that you can do something to help yourself feel better if you are feeling blue?
4. As compared with other people with arthritis like yours, how certain are your that you can manage arthritis pain during your daily activities?
5. How certain are you that you can manage your arthritis symptoms so that you can do the things you enjoy doing?
6. How certain are you that you can deal with the frustration of arthritis?

*** Each question is followed by the scale:**



Each subscale is scored separately, by taking the mean of the subscale items. If one-fourth or less of the data are missing, the score is a mean of the completed data. If more that one-fourth of the data are missing, no score is calculated.

Appendix 20: Pittsburgh Sleep Quality Index and permission

Instructions:

The following questions relate to your usual sleep habits during the past 6 weeks only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month.

Please answer all questions.

1. During the past six weeks, when have you usually gone to bed at night?
Usual Bed Time _____

2. During the past six weeks, how long (in minutes) has it usually taken you to fall asleep each night?
Number of Minutes _____

3. During the past six weeks, when have you usually gotten up in the morning?
Usual Getting Up Time _____

4. During the past six weeks, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spend in bed.)
Hours of Sleep Per Night _____

For each of the remaining questions, check the one best response.
Please answer all questions.

5. During the past six weeks, how often have you had trouble sleeping because you:

(a) Cannot get to sleep within 30 minutes

Not during the past month _____	Less than once a week_____	Once or twice a week _____	Three or more times a week _____

(b) Wake up in the middle of the night or early morning

Not during the past month _____	Less than once a week_____	Once or twice a week _____	Three or more times a week _____

(c) Have to get up to use the bathroom

Not during the past month _____	Less than once a week_____	Once or twice a week _____	Three or more times a week _____

(d) Cannot breathe comfortably

Not during the past month _____	Less than once a week_____	Once or twice a week _____	Three or more times a week _____

(e) Cough or snore loudly

Not during the past month _____	Less than once a week_____	Once or twice a week _____	Three or more times a week _____

(f) Feel too cold

Not during the past month _____	Less than once a week_____	Once or twice a week _____	Three or more times a week _____

(g) Feel too hot

Not during the past month _____	Less than once a week_____	Once or twice a week _____	Three or more times a week _____

(h) Had bad dreams

Not during the past month _____	Less than once a week_____	Once or twice a week _____	Three or more times a week _____

(i) Have pain

Not during the past month _____	Less than once a week_____	Once or twice a week _____	Three or more times a week _____

(j) Other reason(s), please describe

_____
_____
_____
_____

How often during the past six weeks have you had trouble sleeping because of this?

Not during the past month _____	Less than once a week_____	Once or twice a week _____	Three or more times a week _____

6. During the past six weeks, how would you rate your sleep quality overall?

Very good _____	Fairly good _____	Fairly bad _____	Very bad _____

7. During the past six weeks, how often have you taken medicine (prescribed or "over the counter") to help you sleep

Not during the past month _____	Less than once a week_____	Once or twice a week _____	Three or more times a week _____

8. During the past six weeks, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month _____	Less than once a week_____	Once or twice a week _____	Three or more times a week _____

9. During the past six weeks, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____
Only a very slight problem _____
Somewhat of a problem _____
A very big problem _____

10. Do you have a bed partner or roommate?

No be partner or roommate _____
Partner/roommate in other room _____
Partner in same room, but not same bed _____
Partner in same bed _____

If you have a roommate or bed partner, ask him/her how often in the past month you have had….

(a) Loud snoring

Not during the past month _____ | Less than once a week_____ | Once or twice a week _____ | Three or more times a week _____

(b) Long pauses between breaths while asleep

Not during the past month _____ | Less than once a week_____ | Once or twice a week _____ | Three or more times a week _____

(c) Legs twitching or jerking while asleep

Not during the past month _____ | Less than once a week_____ | Once or twice a week _____ | Three or more times a week _____

(d) Episodes of disorientation or confusion during sleep

Not during the past month _____ | Less than once a week_____ | Once or twice a week _____ | Three or more times a week _____

(e) Other restlessness while you sleep, please describe

_____
_____
_____

Not during the past month _____ | Less than once a week_____ | Once or twice a week _____ | Three or more times a week _____

Thank You for Completing this Questionnaire

Pittsburgh Sleep Quality Index permission

Dear Ms. Minnock,

You have my permission to use the PSQI for your research study. You can find the instrument, scoring instructions, the original article, links to available translations, and other useful information at www.sleep.pitt.edu under the Instruments tab. Please be sure to cite the 1989 paper in any publications that result.

This copyright in this form is owned by the University of Pittsburgh and may be reprinted without charge only for non-commercial research and educational purposes. You may not make changes or modifications of this form without prior written permission from the University of Pittsburgh. If you would like to use this instrument for commercial purposes or for commercially sponsored research, please contact the Office of Technology Management at the University of Pittsburgh at 412-648-2206 for licensing information.

Good luck with your research.

Sincerely,

Daniel J. Buysse, M.D.
Professor of Psychiatry and Clinical and Translational Science
University of Pittsburgh School of Medicine
E-1127 WPIC
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F: (412) 246-5300
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Appendix 21: Pittsburgh Sleep Quality Index scoring sheet

Form Administration Instructions, References, and Scoring

(University of Pittsburgh 2010)

The range of values for questions 5 through 10 are all 0 to 3.

Questions 1 through 9 are not allowed to be missing except as noted below. If these questions are missing then any scores calculated using missing questions are also missing. Thus it is important to make sure that all questions 1 through 9 have been answered.

In the event that a range is given for an answer (for example, '30 to 60' is written as the answer to Q2, minutes to fall asleep), split the difference and enter 45.

Reference

Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ: The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Research* 28:193-213, 1989.

Scores – reportable in publications

On May 20, 2005, on the instruction of Dr. Daniel J. Buysse, the scoring of the PSQI was changed to set the score for Q5J to 0 if either the comment or the value was missing. This may reduce the DISTB score by 1 point and the PSQI Total Score by 1 point.

PSQIDURAT **DURATION OF SLEEP**

IF Q4 ≥ 7, THEN set value to 0
IF Q4 < 7 and ≥ 6, THEN set value to 1
IF Q4 < 6 and ≥ 5, THEN set value to 2
IF Q4 < 5, THEN set value to 3
Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQIDISTB **SLEEP DISTURBANCE**

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) = 0, THEN set value to 0

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) ≥ 1 and ≤ 9, THEN set value to 1

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) > 9 and ≤ 18, THEN set value to 2

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) > 18, THEN set value to 3

Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQILATEN **SLEEP LATENCY**

First, recode Q2 into Q2new thusly:
IF Q2 ≥ 0 and ≤ 15, THEN set value of Q2new to 0
IF Q2 > 15 and ≤ 30, THEN set value of Q2new to 1
IF Q2 > 30 and ≤ 60, THEN set value of Q2new to 2
IF Q2 > 60, THEN set value of Q2new to 3
Next
IF Q5a + Q2new = 0, THEN set value to 0
IF Q5a + Q2new ≥ 1 and ≤ 2, THEN set value to 1
IF Q5a + Q2new ≥ 3 and ≤ 4, THEN set value to 2
IF Q5a + Q2new ≥ 5 and ≤ 6, THEN set value to 3

Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQIDAYDYS **DAY DYSFUNCTION DUE TO SLEEPINESS**

IF Q8 + Q9 = 0, THEN set value to 0
IF Q8 + Q9 ≥ 1 and ≤ 2, THEN set value to 1
IF Q8 + Q9 ≥ 3 and ≤ 4, THEN set value to 2
IF Q8 + Q9 ≥ 5 and ≤ 6, THEN set value to 3
Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQIHSE **SLEEP EFFICIENCY**

Diffsec = Difference in seconds between day and time of day Q1 and day Q3

Diffhour = Absolute value of diffsec / 3600
newtib =IF diffhour > 24, then newtib = diffhour – 24
IF diffhour ≤ 24, THEN newtib = diffhour
(NOTE, THE ABOVE JUST CALCULATES THE HOURS BETWEEN GNT (Q1) AND GMT (Q3))
tmphse = (Q4 / newtib) * 100

IF tmphse ≥ 85, THEN set value to 0
IF tmphse < 85 and ≥ 75, THEN set value to 1
IF tmphse < 75 and ≥ 65, THEN set value to 2

IF tmphse < 65, THEN set value to 3
Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQISLPQUAL **OVERALL SLEEP QUALITY**
Q6
Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQIMEDS **NEED MEDS TO SLEEP**
Q7
Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQI **TOTAL**
DURAT + DISTB + LATEN + DAYDYS + HSE + SLPQUAL + MEDS
Minimum Score = 0 (better); Maximum Score = 21 (worse)
Interpretation: TOTAL $\leq$ 5 associated with good sleep quality
TOTAL > 5 associated with poor sleep quality

Appendix 22: Profile of Mood States scoring sheet

POMS S-F Adjectives **Today's Date _____**

Below is a list of words that describe feelings people have.

Please read each one carefully. Then fill in one space for the answer which best describes how you have been feeling during the past week including today.

Depression-dejection

	0 = Not at all	**1 = A little**	**2 = Moderately**	**3 = Quite a bit**	**4 = Extremely**
Unhappy					
Sad					
Blue					
Hopeless					
Discouraged					
Miserable					
Helpless					
Worthless					
				Investigator's use only	

Vigor

	0 = Not at all	**1 = A little**	**2 = Moderately**	**3 = Quite a bit**	**4 = Extremely**
Lively					
Active					
Energetic					
Cheerful					
Full of pep					
Vigorous					
				Investigator's use only	

Anger-hostility

	0 = Not at all	**1 = A little**	**2 = Moderately**	**3 = Quite a bit**	**4 = Extremely**
Angry					
Peeved					
Annoyed					
Grouchy					
Resentful					
Bitter					
Furious					
				Investigator's use only	

POMS S-F Adjectives

Tension-anxiety

	0 = Not at all	**1 = A little**	**2 = Moderately**	**3 = Quite a bit**	**4 = Extremely**
Tense					
On edge					
Uneasy					
Restless					
Nervous					
Anxious					
				Investigator's use only	

Confusion-bewilderment

	0 = Not at all	**1 = A little**	**2 = Moderately**	**3 = Quite a bit**	**4 = Extremely**
Confused					
Unable to concentrate					
Bewildered					
Forgetful					
Uncertain					
				Investigator's use only	

Fatigue-inertia

	0 = Not at all	**1 = A little**	**2 = Moderately**	**3 = Quite a bit**	**4 = Extremely**
Worn out					
Fatigued					
Exhausted					
Weary					
Bushed					
				Investigator's use only	

Thank you for completing this questionnaire

Appendix 23: Beck Depression Inventory

Please read each group of statements carefully. Then pick out the one statement from each group which best describes the way you have been feeling the past two weeks, including today. Circle the number beside the statement you picked. If several statements in the group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

0 I do not feel sad.
1 I feel sad.
2 I am sad all the time and I can't snap out of it.
3 I am so sad or unhappy that I can't stand it.

0 I am not particularly discouraged about the future.
1 I feel discouraged about the future.
2 I feel I have nothing to look forward to.
3 I feel that the future is hopeless and that things cannot improve.

0 I do not feel like a failure.
1 I feel I have failed more than the average person.
2 As I look back on my life, all I can see is a lot of failures.
3 I feel I am a complete failure as a person.

0 I get as much satisfaction out of things as I used to.
1 I don't enjoy things the way I used to.
2 I don't get real satisfaction out of anything any more.
3 I am dissatisfied or bored with everything.

0 I don't feel particularly guilty.
1 I feel guilty a good part of the time.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

0 I don’t feel disappointed in myself.
1 I am disappointed in myself.
2 I am disgusted with myself.
3 I hate myself.

0 I don’t feel I am any worse than anybody else.
1 I am critical of myself for my weaknesses or mistakes.
2 I blame myself all the time for my faults.
3 I blame myself for everything bad that happens.

0 I don’t have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

0 I don’t cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can’t cry even though I want to.

0 I am no more irritated now than I ever am.
1 I get annoyed or irritated more easily than I used to.
2 I feel irritated all the time now.
3 I don’t get irritated at all by the things that used to irritate me.

0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions than before.
3 I can’t make decisions at all anymore.

0 I don’t feel I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance that make me look unattractive.
3 I believe that I look ugly.

0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than usual and find it hard to get back to sleep.

0 I don't get more tired than usual
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all any more.

I am purposely trying to lose weight by eating less YES __ NO__

0 I haven't lost much weight, if any, lately.
1 I have lost more than 5 pounds.
2 I have lost more than 10 pounds.
3 I have lost more than 15 pounds.

0 I am no more worried about my health than usual.
1 I am worried about physical problems such as aches or pains; or upset stomach; or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think about anything else.

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

Appendix 24: Beck Hopelessness Scale

BHS

		True	False
1	I look forward to the future with hope and enthusiasm.		
2	I might as well give up because I can't make things better for myself.		
3	When things are going badly, I am helped by knowing they can't stay that way forever		
4	I can't imagine what my life would be like in 10 years.		
5	I have enough time to accomplish the things I most want to do.		
6	In the future, I expect to succeed in what concerns me most.		
7	My future seems dark to me.		
8	I expect to get more of the good things in life than the average person.		
9	I just don't get the breaks, and there's no reason to believe I will in the future.		
10	My past experiences have prepared me well for the future.		
11	All I can see ahead of me is unpleasantness rather than pleasantness.		
12	I don't expect to get what I really want.		
13	When I look ahead to the future, I expect I will be happier than I am now.		
14	Things just don't work out the way I want them to.		
15	I have great faith in the future.		
16	I never get what I want so it's foolish to want anything.		
17	It is very unlikely that I will get any real satisfaction in the future.		
18	The future seems vague and uncertain to me.		
19	I can look forward to more good times than bad times.		
20	There is no use in really trying to get something I want because I probably won't get it.		

Thank you for completing this questionnaire

Appendix 25: Beck Depression Inventory and Beck Hopelessness Scale scoring guidance

PSYCHOMETRIC SCALE SCORING GUIDANCE

To enable you to see how they may be used in practice, guidance is given below as to how to score each measure.

Beck Depression Inventory (BDI)

Rate each answer as indicated on the measure, ie each question scores between 0-3 and the total score is the summation of answers to all the questions.

total score	*level of depression*
< 13	minimal
14 – 19	mild
20 – 28	moderate
> 29	severe

Beck Hopelessness Scale (BHS)

The BHS total is derived by summing the scores for each of the 20 questions. Each question is answered with either a **T** (True) or **F** (False).

Score 1 for T on 2, 7, 9, 11, 12, 14, 16, 17, 18, 20

Score 1 for F on 1, 3, 4, 5, 6, 8, 10, 13, 15, 19

total score	*level of hopelessness*
< 3	minimal
4 – 8	mild
9 – 14	moderate
> 14	**severe**

Appendix 26: Semi-structured qualitative interview

1. ***Description of fatigue from the patients perspectives-Prompts:***

   In your own words tell me what fatigue means to you

   What way might you describe your fatigue to your doctor or nurse?

   Have you experienced different levels of fatigue, and how would you describe this to your doctor?

   Can you have different types of fatigue throughout a day or a week?

2. ***Causes of fatigue from the patients perspectives-Prompts:***

   What do you think causes this fatigue?

   Tell me about your lifestyle- (work/social/leisure/relaxation/ components)

   What if any keep fit activity/exercise can you manage/like to do/try to do?

   Might there be a link between your fatigue and your own personality or mood?

   Could there be a link between your fatigue and medication- why do you think so?

3. ***Impact of fatigue -Prompts:***

   Tell me how fatigue affects you physically/ day to day activities/home life/work life outside of home

   How does your fatigue effect your mood/emotions

   What effect if any does your fatigue have on your family?

   Have you ever noticed if fatigue has any effect your concentration?

   If you are making plans do you factor in fatigue?

4. ***Management of fatigue from the patients perspectives-Prompts:***

   What do you do to manage your fatigue?

   What advice have you ever got from your doctor or nurse?

   How would advise others to deal with fatigue?

   How would you suggest doctors/nurse advise patients about fatigue?

Appendix 27: Ethical approval: Host hospital

[redacted] Healthcare GROUP LIMITED [redacted]

Ethics and Medical Research Committee

[redacted]

Tel. [redacted] Fax [redacted] email: [redacted]

4/4/07

[redacted]

Re: Fatigue in inflammatory rheumatic diseases: Identifying contributory factors, patients' perceptions of fatigue and potential self-management interventions. PIL/Consent Form version 2 April 2007

Dear [redacted],

Thank you for the revised PIL/Consent that was requested prior to approval at the Ethics and Medical Research Committee meeting held on Wednesday 7th March, 2007 at which the above study was reviewed.

This study is now approved.

Yours sincerely,

[redacted]

Chairman,
Ethics and Medical Research Committee.

cc. Ms. P. Minnock, Advanced Nurse Practitioner, [redacted]

[redacted] Healthcare GROUP LIMITED [redacted]

Ethics and Medical Research Committee

[redacted]

9/4/07

Ms. P. Minnock
[redacted]

Re: Fatigue in inflammatory rheumatic diseases: Identifying contributory factors patient's perceptions of fatigue and potential self management interventions.
Phase 3 of study: Participant information/Consent Form Phase 3. Interview Schedule.

Dear Ms. Minnock, Patricia

The above amendment was reviewed at the Ethics and Medical Research Committee meeting held on Wednesday 4th April, 2007.

This amendment was approved.

Yours sincerely,

[redacted]

Chairman,
Ethics and Medical Research Committee.

Appendix 28: Ethical permission University of Dublin, Trinity College Dublin

THE UNIVERSITY OF DUBLIN
TRINITY COLLEGE

SCHOOL OF MEDICINE
FACULTY OF HEALTH SCIENCES

Trinity College, Dublin 2, Ireland
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Professor Dermot Kelleher, MD, FRCPI, FRCP, F Med Sci
Head of School of Medicine
Vice Provost for Medical Affairs

Ms Fedelma McNamara
School Administrator
email: fmcnamar@tcd.ie

Ms P Minnock
Advanced Nurse Practitioner
[redacted]

Friday, 31 August 2007

Study: A mixed methods study to determine contributing factors and patients perceptions of fatigue in inflammatory arthritis

Dear Applicant

Further to a meeting of the Faculty of Health Sciences Research Ethics Committee 2006 - 2007, we are pleased to inform you that the above project has been approved without further audit.

Yours sincerely

pp Noelle Costelloe.
Dr Orla Sheils
Chairperson
Faculty of Health Sciences Research Ethics Committee

cc. Supervisor: Prof Begley