INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps. Each original is also photographed in one exposure and is included in reduced form at the back of the book.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

UMI®

Bell & Howell Information and Learning
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA
800-521-0600

NOTE TO USERS

This reproduction is the best copy available.

UMI®

Clinical and Health Status of Patients with Systemic Lupus Erythematosus: The Impact of Disease Activity, Damage and other Clinical Measures

Chenchen Wang

Department of Epidemiology and Biostatistics

McGill University, Montreal ,QC

May, 1999

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfilment of the requirements for the degree of Master of Science

© Chenchen Wang , 1999

National Library of Canada
Acquisitions and Bibliographic Services
395 Wellington Street
Ottawa ON K1A 0N4
Canada

Bibliothèque nationale du Canada
Acquisitions et services bibliographiques
395, rue Wellington
Ottawa ON K1A 0N4
Canada

Your file Votre référence

Our file Notre référence

The author has granted a non-exclusive licence allowing the National Library of Canada to reproduce, loan, distribute or sell copies of this thesis in microform, paper or electronic formats.

The author retains ownership of the copyright in this thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without the author's permission.

L'auteur a accordé une licence non exclusive permettant à la Bibliothèque nationale du Canada de reproduire, prêter, distribuer ou vendre des copies de cette thèse sous la forme de microfiche/film, de reproduction sur papier ou sur format électronique.

L'auteur conserve la propriété du droit d'auteur qui protège cette thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

0-612-55096-6

Canada

To my Dear Father San Lin Wang

ABSTRACT

The prognosis of Systemic Lupus Erythematosus (SLE) has improved markedly over recent decades, however, little research has focused on the improvement of SLE patient's quality of life. The main objective of this cross-sectional study was to evaluate the relationship between disease activity, cumulative damage and self-reported quality of life in 54 patients with SLE.

Disease activity was measured by the SLE Disease Activity Index (SLEDAI), Systemic Lupus Activity Measure (SLAM-2) and cumulative damage by the Systemic Lupus International Cooperating Clinics/ACR damage index (DI). Quality of life was assessed by the Medical Outcome Survey Short Form 36 (SF-36) and the Euroqol (EQ-5D) self-report questionnaires. Multiple linear regression was used to identify significant predictors of patients' self reported health status. Cumulative damage was found to be associated with physical function, physical health and social functioning (SF-36); disease activity was found to have a significant association with general health (SF-36) and a weaker association on overall health status as evaluated through the 'thermometer' rating scale of the EQ-5D. Patients' ratings of ability with usual activities was strongly related to overall physical health (SF-36) as well as the physical functioning and general health sub-scales of the SF-36. In addition, patients' ratings of anxiety and depression were strongly related to overall mental health status (SF-36).

In conclusion, physical health of SLE patients was associated with disease activity, disease damage, capacity for usual activity, and mobility.

Abrégé

L'espérance de vie des patients atteints du Lupus Erythemateux Disséminé (LED) s'est améliorée de manière significative depuis 25 ans. Toutefois, peu de recherches se sont penchées sur l'amélioration de la qualité de vie des patients atteints de cette maladie. L'objectif principal de cette étude transversale était d'évaluer la relation entre le niveau d'activité de la maladie, le dommage résiduel résultant de cette maladie, et la qualité de vie tel que rapportés par 54 patients atteints de LED.

Le niveau d'activité de la maladie était mesuré par le 'SLE Disease Activity Index' (SLEDAI) et le 'Systemic Lupus Activity measure' (SLAM-2). Le dommage résiduel résultant de cette maladie était mesuré par le 'Systemic Lupus International Cooperating Clinics/ACR damage index (DI)'. La qualité de vie des 54 patients était évaluée par le 'Medical Outcome Survey Short Form 36 (SF-36)' et le 'Euroqol questionnaire (EQ-5D)'. La technique de régression linéaire multiple a été utilisée afin d'identifier la les association de ces variables dans la détermination des évaluations que faisaient les patients de leur propre état de santé globale.

Les résultats démontrent que le dommage résiduel influence fortement la fonction physique, la santé physique et le fonctionnement social. Le niveau d'activité de la maladie, évalué par le SF-36, avait une association significative des évaluations d'états de santé globale que faisaient les patients. Cette même variable avait une faible association lorsqu'elle était évaluée par l'échelle de type thermomètre du EQ-5D. Les propres évaluations des patients sur leur capacité à exécuter leurs activités habituelles avaient une

forte association avec de l'état de santé physique globale tel qu'évalué par le SF-36, ainsi que les sous-échelles de fonctionnement physique et santé globale du SF-36. De plus, les estimations d'anxiété et de dépression avaient une forte association avec la santé mentale (SF-36).

En concluant, le niveau d'activité de la maladie, le dommage résiduel résultant du LED, la capacité d'entreprendre des activités habituelles, et la mobilité étaient tous associés à la santé physique des patients atteints de LED.

ACKNOWLEDGEMENTS

I would like to respectfully thank my supervisor, Dr. Nancy Mayo, whose assistance, guidance, and availability over the past two years made her the key to the successful completion of my Master's degree in Epidemiology.

I would also like to express my gratitude to my advisor Dr. Paul Fortin, who despite his busy schedule, committed both time and energy to provide valuable input and guidance in the writing of this manuscript and proof-reading of my thesis.

I extend a special acknowledgement to Claudette Corrigan, for her constant accessibility, assistance, and encouragement. I am grateful to Véronique Benk for her help with the English to French translation of the patient consent form. Thanks also to Dr. Nancy Mayo' s other students: Nancy Salbach, Sara Ahmed, Adriana Venturini, their friendly help for this thesis was greatly appreciated.

I would also like to thank the study nurses, Carolyn Neville for her assistance with patient evaluations, data collection, and preparation. The kindly assistance of Diane Ferland and Sonia Mata who facilitated the data entry in the Medlog software, adaptation of the database, as well as preparation of the data. The help and advice of Dr Michal Abrahamowicz was also greatly appreciated as was the computer programming assistance of Susan Scott, Adrian Levy, and Gillian Bartlett.

I also gratefully acknowledge the financial assistance provided to me through the "Fonds pour la Formation de Chercheurs et l' Aide à la Recherche," FRSQ-FCAR throughout my Master's degree.

It would be remiss not to mention the support and encouragement provided by all of the doctors and nurses in the Lupus Clinic and Clinical Epidemiological Department at the Montreal General Hospital.

I wish to thank my dear father, mother, brother and sisters in China, as well as my lovely daughter Xiaoyan Chen, for the way they encouraged me to always do my best, and all of many other dear friends and fellow graduate students, for their friendly help, encouragement and concern.

Finally, I would like to thank all the study participants who were willing to fill out my entire questionnaires. All would have been impossible without these patients.

TABLE OF CONTENTS

APPENDIX B: (Continued)

LIST OF TABLES

LIST OF FIGURES

GLOSSARY

Term	Definition
Disease Activity	"the reversible manifestations of the underlying inflammatory and immunologic processes which can be expressed as individual clinical or laboratory features (Bombardier et al., 1992)."
Disease Damage	"the irreversible impairment, which was defined as being continuously persistent for at least 6 months (Stoll et al.,1996)."
Health -Related Quality of Life	"a measure of the value assigned to duration of life as modified by impairments, functional states, perceptions and opportunities, as influenced by disease, injury, treatment and policy (Patrick and Erickson,1993)".
Impairment	"any loss or abnormality of psychological, physiological or anatomical structure or function (WHO, 1980)."
Disability	"any restriction or lack of ability to perform an activity in the manner or within the range considered normal for a human being (WHO, 1980)."
Handicap	"a disadvantage for a given individual ,resulting from an impairment or a disability, that limits or prevents the fulfilment of a role that is normal for that individual (WHO, 1980)."

PREFACE

Regulations for a Manuscript-Based Thesis
Faculty of Graduate Studies and Research
McGill University

The Faculty of Graduate Studies and Research (FGSR) of McGill University requires that the first five paragraphs of the Guidelines for Thesis Preparation be reproduced in the Preface section of this thesis. This is necessary to inform the external examiner that the regulations regarding originality and co-authorship do not apply to this thesis.

"1. Candidates have the option of including, as part of the thesis, the text of one or more papers submitted, or to be submitted for publication, or the clearly-duplicated text (not the reprints) of one or more published papers. These texts must conform to the Thesis Preparation Guidelines with respect to font size, line spacing and margin sizes and must be bound together as an integral part of the thesis.

2. The thesis must be more than a collection of manuscripts. All components must be integrated into a cohesive unit with a logical progression from one chapter to the next. In order to ensure that the thesis has continuity. Connecting texts that provide logical bridges between the different papers are mandatory.

3. The thesis must conform to all other requirements of the "Guidelines for thesis preparation" in addition to the manuscripts. The thesis must include the following: a table of contents; an abstract in English and French; an introduction which clearly states the rationale and objectives of the research, a comprehensive review of the literature; a final conclusion and summary; and, rather than individual reference lists after each chapter or paper, one comprehensive bibliography or reference list, at the end of the thesis, after the final conclusion and summary.

4. As manuscripts for publication are frequently very concise documents, where appropriate, additional material must be provided (e.g. appendices) in sufficient detail to allow a clear and precise judgement to be made of the importance and originality of the research reported in the thesis.

5. In general, when co-authored papers are included in a thesis the candidate must have made a substantial contribution to all papers included in the thesis. In addition, the

candidate is required to make an explicit statement in the thesis as to who contributed to such work and to what extent. This statement should appear in the single section entitled " Contributions of Authors" as a preface to the thesis. The supervisor must attest to the accuracy of this statement at the doctoral oral defence. Since the task of the examiners is made more difficult in these cases, it is in the candidate's interest to clearly specify the responsibilities of all the authors of the co-authored papers."

Organization of the Thesis

In the first chapter the introduction and rationale for the research project is presented. Chapter two contains background material related to SLE and it's clinical picture. The concept of disease activity, disease damage and their measurement and implications are discussed. Also the relationship between disease activity and damage and health status is reviewed.

The principal objectives of this research project are presented in chapter three.

The manuscript is found in chapter 4. The manuscript is written in the style recommended for the journal entitled " Journal of Rheumatology". As the FGSR of McGill University requires a literature review separate from the one found in the manuscript, some duplication of material was unavoidable.

Chapter 5 discusses the results presented in the manuscript and draws final conclusions. Suggestions for future studies are also made.

Supplementary information regarding the methods used in the project, including a detailed description of the instrumentation material, which is not normally presented in a manuscript prepared for a journal, is presented in the appendices at the end of the thesis.

Ethical Considerations

A number of precautions were taken to protect the rights of eligible subjects for this study: 1) a formal ethical review of the entire project was obtained; 2) informed consent was obtained (see appendix C); 3) confidentiality of the data was ensured and 4) a phone number was provided to participants who wished to call and obtain more information.

The person's desire or not to participate in the study was not immediately communicated to the treating physician as this may have altered physicians' modes of documenting disease status. Furthermore, the patient may have felt that their non-participation could have influenced the doctor-patient interaction and their care. The data collected during the clinical visit for persons not willing to participate was not made available to the researchers.

Potential subjects were assured that their participation was voluntary, there were no known hazards from their participation, they could withdraw from the study at any time, and their questions would be answered. All information was treated with anonymity and confidentiality, using a numerical code on all data sheets and computer entries. A list with names with corresponding codes was kept locked in the office. All data collected during the interviews were kept separately from the master file containing the identifying information. All paper files were kept in locked filing cabinets in a room that was locked when not in use.

CHAPTER 1

INTRODUCTION

Systemic lupus erythematosus (SLE) is an inflammatory multiorgan chronic disease. Almost invariably, antibodies against nuclear antigens occur, and thus it is classified as an autoimmune disease. SLE exhibits a wide spectrum of clinical manifestations, ranging from mild to severe symptoms. In the former case treatment may not be necessary, however, in the latter, severe symptoms may involve loss of organ function with potentially lethal complications (Mills et al.,1994; Boumpas et al., 1995a; Boumpas et al., 1995b).

The prognosis of SLE has shown a distinct improvement over recent decades and the five year survival rate now approaches or exceeds 90% (Stafford-Brady et al., 1995; Swaak et al., 1989; Reveille et al.,1990; Ward et al., 1995; Abu-Shakra et al.,1995).This increase in the five-year rates of survival is attributed mainly to factors such as, early recognition, more effective therapy, and general advances in the quality of medical care. The fifteen-year survival rate of 63 to 79% (Stafford-Brady et al.,1988; Ward et al., 1995; Abu-Shakra et al., 1995) is less impressive and emphasizes the need for continued efforts to improve long-term outcomes for this disease. As SLE is a chronic disease characterized by multiple exacerbations and remissions, the cornerstone of it's treatment is careful patient monitoring in order to detect flare-ups of disease early enough to allow the prompt institution of appropriate therapy. With improved survival, outcome measures other than

mortality and specific organ function need to be considered in this context, global health status is becoming an increasingly relevant outcome.

The World Health Organizations's (WHO, 1980), Classification of Impairments, Disabilities, and Handicaps (ICIDH) and the concept of health-related quality of life form the theoretical framework for this thesis. These concepts are thought to be hierarchical and aid in the understanding of the impact of disease. The WHO (WHO, 1980) defines impairment as "*any loss or abnormality of psychological, physiological or anatomical structure or function*" and disability as *"any restriction or lack (resulting from an impairment) of ability to perform an activity in the manner or within the range considered normal for a human being".*

Physical disability may contribute to the development of handicap and diminished health-related quality of life. The WHO has defined handicap as " a *disadvantage for a given individual, resulting from an impairment or a disability, that limits or prevents the fulfilment of a role that is normal (depending on age, sex, social and cultural factors) for that individual*".

Health-related quality of life (HRQL) is a broader concept, which appears to be more strongly associated with the level of handicap and disability than of impairment. Although difficult to define, Patrick and associates (Patrick and Erickson, 1993) suggest that health-related quality of life is "*a measure of the value assigned to duration of life as modified by impairments, functional status, and perceptions and opportunities, as*

influenced by disease, injury, treatment and policy". Although SLE may impact on the individual at each of these levels, the focus of the current study is on HRQL and it's components.

The objective of this study, therefore, was to estimate the relationship between health-related quality of life and measures of disease activity, disease damage impairments, disabilities and handicaps in SLE patients.

CHAPTER 2

LITERATURE REVIEW

Epidemiology of Systemic Lupus Erythematosus (SLE)

SLE is a chronic immunologic and inflammatory disease, which occurs worldwide. Studies have shown that its prevalence differs from one part of the globe to another. In the Caucasian population of North America the prevalence is 40 to 50 per 100 000 (Schroeder and Euler, 1997). In European countries, the prevalence ranges from 12.5 per 100 000 in Great Britain to 39 per 100 000 in Sweden (Hochberg, 1990). Results from a recent North American study (McCarty et al., 1995) suggests a high incidence in individuals of African descent. When the rates are compared, an annual incidence of 9.2 per 100,000 for African American women is almost three times greater than an annual incidence of 3.5 per 100,000 found in Caucasian women (McCarty et al.,1995). SLE occurs predominantly in women between the ages of 16 and 42 years (Cervera and Khamashta, 1993) and is approximately 10 times more common in women than men. Epidemiologic studies have also reported (Fessel, 1995; Michet et al., 1985; Hopkinson et al., 1994) that there may be as many as 1 million people with SLE in North America, yielding a prevalence of about 1: 2000. This low prevalence means that the average community based family and general practitioners would have little experience in the management of patients with SLE. SLE is a complex disorder with a variable course and prognosis, which may effect any organ or system or combination of organ, and systems (* Table 2.1 presents common clinical symptoms associated with SLE).

Table 2.1*: FREQUENCY OF CLINICAL SYMPTOMS OF SLE

Symptoms	At Onset (%)	At Any time (%)
Constitutional:		
Fatigue	50	74
Fever	24	40
Weight loss	21	44
Musculoskeletal:		
Arthritis, arthralgia	67	83
Myositis	1	5
Skin:	73	91
Butterfly rash	28	48
Photosensitivity	30	60
Mucous membrane lesion	21	52
Alopecia	32	55
Raynaud's phenomenon	33	60
Purpura	10	34
Urticaria	1	4
Renal:	38	73
Nephrotic syndrome	5	11
Gastrointestinal:	18	44
Pulmonary:	12	23
Pleurisy	17	30
Parenchyma	7	14
Cardiac:	15	20
Pericarditis	8	9
Endocardis	8	11
Myocarditis	1	3
Reticuloendothelial:		
Lymphadenopathy	16	31
Splenomegaly	5	9
Hepatomegaly	2	7
Central nervous system	21	50
Psychosis	1	5
Convulsions	0.5	2
Cranial neuropathies	2	4
Peripheral neuropathies	2	13
Organic brain syndrome	7	15
Transverse myelitis	0	0.5

*Table 2.1 as reported in the Guidelines for the Management of Systemic Lupus Erythematosus in Adults, American College of Rheumatology Ad Hoc Committee on SLE Guidelines, May 1997.

Classification Criteria for SLE

The varied and complex clinical and laboratory manifestations of SLE pose a diagnostic dilemma for clinicians. Criteria have been developed to create a standard reference to help clinicians when they are faced with a potential case of SLE as well as researchers who are concerned exclusively with SLE.

Cohen (Cohen et al., 1971; Cohen and Canoso, 1972) proposed a method of differentiation between major and minor criteria. Using the 14 criteria, proposed by a panel of the American Rheumatism Association (ARA) as those that best portrayed SLE, they found that 90% of the SLE patients met 4 of the 14 criteria and 94% to 96% met 4 or more criteria. The ARA, therefore, recommended that epidemiological or population studies should include only those patients who meet a minimum of 4 criteria. Following this recommendation, a minimum number of criteria to establish a diagnosis of lupus was set at 4.

Subsequent studies of rheumatic diseases revealed that the criteria for SLE over-lapped with the diagnostic criteria for other diseases, e.g. rheumatoid arthritis. In light of this, in 1982, the ARA proposed a revised and improved set of criteria for the classification of SLE. incorporating current immunological knowledge (Tan et al., 1982). The new criteria grouped patients according to the prognosis of SLE. When compared with the 1971 criteria, the revised set showed superior sensitivity (96%) and specificity (96%).These criteria were again revised and updated in 1997 (Hochberg, 1997). Our current study is based on this latest set of revised criteria (Table 2.2).

Table 2.2 Revised Criteria for the Classification of Systemic Lupus Erythematosus (ARA 1982 with revision 1997)

Criteria
1. Butterfly Rash Fixed erythema, flat or raised, over the malar eminencies, tending to spare the nasolabial folds.
2. Discoid Lupus Erythematous raised patches with adherent keratotis scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation.
4. Oral Ulcers Oral or nasopharyngeal ulceration, usually painless, observed by a physician.
5. Arthritis Non-erosive arthritis involving one or more peripheral joints, characterized by tenderness, swelling or effusion
6. Serositis a) Pleuritis-convincing history of pleurtic pain or rub heard by a physician or evidence of pleural effusion b) Pericarditis-documented by ECG or rub or evidence of pericardial effusion.
7. Renal Disorder a) Persistent proteinuria greater than 0.5 grams per day or greater than 3+ if quantitation not performed b) Cellular casts-may be red cell, haemoglobin, granular, tubular, or mixed.
8. Neurologic Disorder a) Seizures-in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance. b) Psychosis in the absence of offending drugs
9. Hematologic Disorder a) Hemolytic anemia- with reticulocytosis. b) Leukopenia-less than 4,000/mm^{3}total on two or more occasions b) Leukopenia-less than 1,500/mm^3 on two or more occasions. c) Thrombocytopenai-less than 100, 000/mm^3 in the absence of offending drugs.
10. Immunologic Disorder a) Anti-DNA-presence of antibody to native DNA inabnormal titer. b) Anti-SM-presence of antibody to Sm nuclesr antigen. c) Positive finding of antiphospholipid antibodies based on 1) an abnormal serum level of IgG or IgM anticardiolopin antibodies, 2) a positive test result for lupus anticoagulant using a standard method, or 3) a false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test.
11. Antinuclear Antibody An abnormal titer of antinuclear antibody for immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with " drug-induced lupus" syndrome.

The Prognosis of SLE

There has been a dramatic increase in research regarding the diagnosis and treatment of SLE. Four decades ago, the majority of individuals diagnosed with SLE died within five years. Most recent studies have noted ten year survival probabilities exceeding 80 percent and it is now approximately 90 percent (Ward et al., 1995; Abu-Shakra et al., 1995). In fact, survival of patients with SLE has increased greatly in the past 20 years (Ginzler and Berg, 1987; Swaak et al.,1989). The marked improvement in survival is a result not only of a broadening of the classification criteria which resulted in the inclusion of milder disease cases in studies of SLE, but also earlier diagnosis, new pharmacologic treatments, greater knowledge about appropriate therapeutic management, and renal dialysis (Boumpas et al., 1995a; Hochberg, 1990; Jonsson et al.; 1989; Pistiner et al., 1991). However, SLE remains a potentially life threatening condition with an unacceptably high mortality rate (Esdaile, 1994).

Patients with SLE must learn to cope with a chronic, life-long disease in which there is always the potential threat of disruptions of normal activities of daily living, serious illness or disability. This challenges both the patient, and their families and health care providers. In ill lupus patients the manifestations are more complex and may require the expertise of professionals in a wide range of fields including, social work, vocational counselling, psychology, physical and occupational therapy, ophthalmology, dermatology, nephology, cardiology, orthopaedic surgery, and other disciplines.

With improved survival, outcome measures other than mortality and specific organ function need to be considered. Patients are demanding improvement in their quality of life and society is trying to decrease disability and health costs and thus Global health status is becoming increasingly relevant in clinical research in SLE.

Clinical Measurement of Systemic Lupus Erythematosus

The outcome of SLE is measured by three concepts covering the following domains: disease activity, cumulative damage and health related quality of life (Bombardier et al., 1992; Fryback and Keeney, 1983).

Global measures of disease activity

Disease activity has been defined by Bombardier et al (Bombardier et al., 1992).as the reversible manifestations of the underlying inflammatory and immunologic processes, which can be expressed as individual clinical (e.g., arthritis, serositis, etc.) or laboratory features (e.g., anti-DNA antibodies or complement levels).

Disease activity is a reflection of the type and severity of organ involvement at any point in time. As pointed out by Decker (Decker, 1982) the ability to assess the degree of disease activity in a patient with SLE is crucial, as many therapeutic decisions are based on the physician's ability to accurately judge disease activity. A "quantitative" measure of disease activity is, therefore, extremely useful in order to monitor changes over the

duration of this disease. Many disease activity indices have been developed (Table 2.3), that vary in the content number of items and ease of use. These indices may be used in the office or clinic to assess and grade the disease activity in an individual patient and to monitor changes in disease activity that may require alterations in therapy.

More than 60 different measures of disease activity in SLE with varying degrees of validation, have been developed (Liang et al., 1988) and earlier studies were inconsistent as to which measurement system was used. No single measures has gained widespread acceptance among investigators for either research or clinical practice (Liang et al., 1988). More recently, some of these indices have been validated and some new instruments have been developed (Table 2.3) (Liang et al., 1989; Symmons et al., 1988; Isenberg et al., 1989; Petri et al., 1992; Gladman et al., 1992).

The first validated index for disease activity in SLE was the Lupus Activity Criteria Count (LACC) (Urowitz et al., 1984) developed to quantify a patient's current level of disease activity. However, the LACC was not useful for monitoring change over time. Since then, several other measures of disease activity have been developed.

The Systemic Lupus Activity Measure (SLAM) was developed in Boston, based on a consensus among the members of the Lupus Council of the American College of Rheumatology in 1989 (Liang et al., 1989). The SLAM includes clinical features of the disease and biochemical markers of global disease processes; it does not include biochemical and immunological tests specific to SLE.

The British Isles Lupus Assessment Group (BILAG) scale was developed

according to the principle of the physician's 'intention to treat (Symmons et al., 1988). The index evaluates disease activity in 8 organ systems using 109 different parameters including results of biochemical tests, however, SLE specific serologic and immunologic tests did not covered. Items are classified as major or minor and scored on a nominal scale: active, progressive, recurrent within 3 months, or absent. The clinician is also asked to judge whether specific treatment is warranted at this time. It has been shown to be a reliable and valid instrument for measuring clinical disease activity in SLE (Liang et al., 1989; Hay et al., 1993; Stoll et al., 1996).

The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) was developed at a conference on prognosis studies in lupus held in Toronto in 1985 (Bombardier et al., 1992; Committee on prognosis studies in SLE, 1986) which included rheumatologists and methodologists from ten centres in North America and Europe.

The SLEDAI includes both clinical and laboratory features of SLE and is weighted to account for "severity". A "weighted" index of 9 organ systems was generated for disease activity in SLE, the SLEDAI, as follows: 8 for central nervous system and vascular, 4 for renal and musculoskeletal, 2 for serosal, dermal, immunologic, and 1 for constitutional and hematologic. The maximum theoretical score is 105, but in practice, few patients have scores greater than 45. The SLEDAI predicted well the physicians' ratings in the testing set (Bombardier et al., 1992; Liang et al.,1988). It is considered a validated model of experience clinicians' global assessments of disease activity in lupus and represents the consensus of a group of experts in the field of research.

The Lupus Activity Index (LAI) (Petri et al., 1989) is a simple measure that does not include specific definitions of disease manifestations but relies solely on the clinician's impression of activity in a particular system. It is a 5-part scale, reflecting disease activity over the previous 2 weeks, which can be completed by the physician in approximately 1 minute. The range of possible LAI scores is 0-3 points.

Another instrument, recently performed by the European Consensus Study Group for Rheumatology Research, is termed the ECLAM (European Consensus Lupus Activity Measurement) (Vitali et al., 1992) which was derived from data pooled from 29 centres, based on the criterion of an optimal approximation of the physician's judgement. It is very similar to the SLEDAI and has been shown a good reliably capture disease activity in SLE (Boumbardieri et al., 1995).

In keeping with these studies, Abrahamowicz et al conducted (Abrahamowicz et al., 1998) a survey of lupus experts to determine at which given disease activity score a randomly selected physician would initiate treatment for a randomly selected patient. The Systemic Lupus Activity Measure (SLAM) (Liang, 1989) and the Systemic Lupus Erythematosus Activity Index (SLEDAI) (Bombardier et al., 1992) scores were used to assess disease activity. The results showed that a SLAM score of 7 was the score at which more than 50% of physicians would treat and that the equivalent SLEDAI score was 6.

Thus, many disease activity indexes have been developed with important differences in their components. In a review of the reliability and validity of six

instruments for the assessment of SLE, Liang (Liang et al., 1989) found that the SLAM, BILAG and SLEDAI had the best inter-visit and inter-rater reliability. They have better psychometric properties than the others for clinical research and they have been shown to correlate well with physicians' global assessment of disease activity.

Table 2.3 Indices of Disease Activity

Indices	Content	No of items	Severity Score	Range in Score
Systemic Lupus Activity Measure (SLAM)	Constitutional, Visual, Joints, Reticuloendothelial, Pulmonary, Cardiovascular Gastrointestinal Neuromotor, Laboratory	31	Variable	0-84
Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)	Seizure, Psychosis, Visual, Organ Brain Syndrome, Cranial Nerve, Lupus headaches, CVA, Vasculitis, Arthritis, Myositis, Casts, haematuria Proteinuria, New Rash, Alopecia, Mucous, membrane, Pericarditis, Laboratory	24	Fixed	0-105
British Isles Lupus Activity Group (BILAG)	Constitutional, skin, vasculitis CNS, arthritis, hematology, renal, pleuropulmonary	109	Variable	0-72
European Consensus Lupus Activity Measurement (ECLAM)	Psychosis, seizure, Organ Brian Syndrome. CNS, Rash, Alopecia, Pleurisy, Laboratory	24	Variable	0-17.5
Lupus Activity Index (LAI)	Part 1: physician rated disease activity on a VAS Part 2: fatigue, rash, joint involvement, serositis Part 3: neurologic, renal, pulmonary and hematologic Part 4: medication use Part 5: laboratory variables	5	Variable	0-3-points

Global Measures of Disease Damage in SLE

The inflammatory process in SLE is the underlying construct measured by scales of disease activity and is the mechanism leading to irreversible organ damage. Disease activity, which is continually persistent for at least 6 months (Stoll et al.,1996) will produce organ damage. In order to measure the cumulative damage, the Systemic Lupus International Collaborative Clinics /American College of Rheumatology Damage index (SLICC/ACR DI) was developed in 1992 (Stoll et al., 1996). It has been validated and subsequently showed good inter observer reliability (Gladman et al., 1992; Gladman et al., 1996).

The SLICC /ACR DI summarizes cumulative damage in 12 organs or systems: ocular (range of scores: 0-2), neuropsychiatric (0-6), renal (0-3), pulmonary (0-5), cardiovascular (0-6), musculoskeletal (0-6), dermatological (0-3), gonadal (0-1), diabetes (0-1) and malignancy (0-2). Each item must be present for 6 consecutive months in order to be scored. The total SLICC/ACR DI score can range from 0 (no damage) to 46 (maximum damage) but will, in fact, rarely exceed 10.

The SLICC/ACR DI has now been applied to assess damage in a large number of patients with SLE. Patients with higher initial damage scores have a worse prognosis for survival. The damage index may thus provide an important outcome measure in SLE, both for studies of prognosis and in the assessment of the long-term effects of disease activity and therapy (Gladman et al., 1994).

Measures of Health Related Quality of Life (HRQL) in SLE

In general, Health Related Quality of Life (HRQL) refers to an individual 's overall sense of physical, social, and emotional well being (Naughton and Shumaker,1997; Testa and Simonson, 1996). HRQL measures reflect the patient's evaluation of the impact across many dimensions that a disorder or health problem has on his or her life.

This more holistic concern for the outcomes of health care has prompted a large body of research. It's measurement is increasingly accepted as an important element in assessing medical intervention. In 1991, Guyatt (Guyatt et al.,1991) offered the following all encompassing definition of this concept: *"all those things that one might want to measure about the health of an individual beyond death and physiologic measures of disease activity*" . Liang (Liang, 1987) states that *" HRQL reflects the recognition that a patients' integrated perception of health is not to be viewed only from a biological point of view, but also from its psychological and social consequences.*``

Ultimately, what constitutes ' Quality of Life' is bound by culture. However, a recent conference composed of an international group of HRQL investigators reached agreement on the fundamental dimensions essential to any HRQL assessment (Naughton and Shumaker, 1997). These primary dimensions include physical, sychological and social functioning, role activities, overall life satisfaction, and perception of health status.

This redefinition of the scope of health implies that the evaluation of medical interventions and health care systems in general should take into account not only the

duration of an individual life, but also the degree to which that life is enjoyed or endured. There is little doubt that the measurement of health status and health related quality of life (HRQL) is important in the evaluation of SLE.

Surprisingly, there have been relatively few studies of the HRQL in persons with SLE. Indeed, some studies found no evidence of improved survival prognosis amongst patients with improved. quality of life (Stein et al., 1986; Karlson et al., 1997). The modern challenge for rheumatologists is to improve quality as well as duration of life (Fortin et al.,1998). In order to improve quality of life in SLE, it must first be defined, recognized, and measured. This important construct has been assessed by two instruments in our study: the Medical Outcomes Study: Short form 36 (SF-36) and the EuroQoL; EQ-5D (Ware and Sherboune, 1992; The EQ-5D group, 1990).

In fact, valid and reliable instruments have been successfully developed in the past for rheumatologic disorders (Felson et al.,1993; Ruta et al.,1998; Stock et al., 1996; Deyo et al., 1994) and have been shown to have better reproducibility than tests of physical diagnosis, x-ray or EMG (Deyo, 1988; Feinstein et al., 1986). The SF-36 and the SF-20, (a shorter version of the well-known SF-36) have also been shown to be valid and reliable for the evaluation of HRQL of SLE (Stewart et al.,1988; Gladman et al., 1996). Relatively little is known, however, about how well patients' self-rated HRQL and physicians' ratings for disease activity and damage concur. This is important because physicians base treatment on activity and damage and patients rate the success of this treatment against how they feel.

Relationship between Disease Activity, Damage and HRQL

The measurement of both reversible and permanent impairment, respectively termed disease activity and disease damage, are cornerstones of the assessment of SLE patients. It is also well known that measures of quality of life that allow the expression of the physical, psychological, mental, and social aspects of experience with SLE are sufficiently comprehensive to cover all the dimensions of quality of life that patients consider relevant (Carr et al., 1996). Six recent studies (Tables 2.4a, 2.4b) have examined the relationships between disease activity, damage and HRQL.

Hanly (Hanly, 1997) conducted a cross-sectional study of 96 SLE patients to examine the relationship between disease activity scores (SLEDAI), disease damage scores (SLICC/ACR DI) and patients self-reported quality of life scores (HRQL). No correlation was found between disease activity and disease damage scores or between either of these scores and any of the six sub-scales scores of the SF-20 quality of life measure. The author concludes that the extent of inflammatory disease activity and irreversible target organ damage are, therefore, not the sole determinants of quality of life in SLE patients.

Gladman's work out of Toronto (Gladman et al.,1996; Gladman et al.,1996) also found no correlation between disease activity and disease damage or between either of disease activity or damage and any of several quality of life instruments included. The authors also conclude that these three outcomes, disease activity, disease damage, and

health status remain three important independent outcome measures in the assessment of prognosis in lupus patients.

In contrast, Stoll et al (Stoll et al.,1997) found that different levels of disease severity were associated with different quality of life scores and, in particular, disease activity had a greater effect on quality of life than, age, and cumulative damage and disease duration. Burkhardt (Burkhardt et al.,1992) also found that disease activity was associated with HRQL in a group of SLE patients followed prospectively.

In Fortin' s study (Fortin et al., 1998), 96 patients with lupus were tested to verify if lupus activity or damage would predict physical function and general health. They found disease activity and cumulative damage only measure a small part of the overall picture in lupus. Disease activity shows to be an important correlate of poor physical function at baseline. Change in the level of disease activity negatively correlates with change in quality of life (high disease activity is associated with low HRQL and vice-versa).

The overall conclusion from these studies is that disease activity, irreversible organ damage, and HRQL are, at least to some extent, independent measures of the impact of SLE.

These findings suggest that clinicians and patients can hold differing views of what factors are important in the experience of SLE.

Given the differing results as to the relationships among key variables in SLE, the present study was carried out to add a further dimension to the measurement of the consequences of SLE, that of global health status. The combined information of disease activity, damage, HRQL, global health rating will provide a more complete portrait of the impact of SLE on the lives of those affected and on the relationships among these various dimensions.

Table 2.4 a: Relationship between Disease Activity, Damage and HRQL

Authors Type of Study	Outcome	No of patients With SLE	Measures	Results
Hanly JG Canada 1997 Cross-sectional Study	SF-20	96	Disease activity SLEDAI Disease damage *SLICC/ACR DI	No correlation Between SLEDAI, Cumulative damage, and SF-20 subscales
Gladman DD Canada 1996 (May) Cross-sectional Study	SF-20	105	Disease activity *SLEDAI Disease damage SLICC/ACR DI	1) No correlation between SLEDAI and SLICC/ ACR DI. 2) No correlation between SLICC/ACR DI and any of SF-20 domains by Pearson correlation. 3) Although a statistical correlation was demonstrated between the SLEDAI and two domains of the SF-20 (social functioning and health perception), but there were not clinically important.
Gladman DD Canada 1996 (June) Cross-sectional Study	Five health status Instruments * (FSS, DDM, HAQ, CES-D, SF-20)	125	Disease activity SLEDAI	No correlation between any of the instruments used and the disease activity.

Table 2.4 b : Relationship between Disease Activity, Damage and HRQL (continued)

Authors Type of Study	Outcome	No of patients With SLE	Measures	Results
Burckhardt CS. Sweden 1992 Prospective Study	The Quality of Life Scale	50 (50 RA)	Disease activity *RAI *SLAM	Disease activity was associated with HRQL
Stoll T UK. England 1997 Cross-sectional Study	SF-36 SF-20	150	Disease activity * BILAG Disease damage SLICC/ACR DI	Significant associations between HRQL and with disease activity, and different disease activity levels were significantly associated with different HRQL scores
Fortin P Canada 1998 Prospective Study	SF-36 and HAQ	96	Disease activity SLAM-R and SLEDAI Disease damage SLICC/ACR DI	1) Baseline activity score as measured by SLAM-R are correlated with most sub-scales of SF-36. 2) Baseline damage scores correlated only with HAQ and the physical function subscales of SF-36. 3) Differences in both activity measures over time correlated with change in health status measures. 4) Change in lupus activity measures (SLAM and SLEDAI) reflected change in patient's health status performance over time.

Abbreviations
SF-36: the MOS Short Form 36, SF-20: the MOS Short Form 20.
FSS: the Fatigue Severity Scale; DDM: the Disability Days Measure;
HAQ: the Health Assessment Questionnaire;
CES-D: the Centre for Epidemiological Studies-Depression Scale;
MOS: the Medical Outcome Study.
RAI: Ritchie Articular Index.
SLAM: Systemic Lupus Activity Measure.
AIMS: the Arthritis Impact Measurement Scales.
SLEDAI: SLE Disease Activity Index.
BILAG: the British Isles Lupus Activity Group System
SLICC/ACR DI: the Systemic Lupus International Collaborating Clinics/ American College of Rheumatology Damage Index

Relevance

In chronic disease, such as SLE, the subjective evaluation that patients make of their health may not correspond with its objective assessment by physicians. This discrepancy may also be found concerning the effects of a health intervention. One explanation is that, whereas physicians tend to concentrate on the biological and physiological components of disease, patients' self reports reflect an integrated perception which include the biological, psychological, and social dimensions of their health (Naughton and Shumaker, 1997). Patients' self-reports provide privileged information about how disease and treatment are experienced. This is an intimate part of their 'private' reality, which is not otherwise accessible to the external observer. It has even been suggested that subjective assessment of global health could be an even more sensitive monitor of health status than external measures. It is argued (Testa and Simonson, 1996) that clinicians' consideration of patients' self reports could result in higher patient satisfaction, improved clinical outcomes, and improved treatment compliance by assisting patients and clinicians in understanding each other's point of view about the disease processes.

Valid and reliable instruments, easy to administer and inexpensive to process, exist for the measurement of HRQL. Two such instruments are Medical Outcome Study 36-item Short-Form health survey (SF-36) (Ware and Sherbourne, 1992) and the Euroqol (EQ-5D) (The EuroQol Group, 1990). Several studies have related disease and activity and damage to HRQL using the SF-36 or SF-20; none have included the EQ-5D, which

covers domains of impairment, disability and handicap as well as a global assessment of overall health status. We feel that our study will provide valuable information concerning the relationship between measures of disease activity and health related quality of life. Such information should help clinicians when faced with the dilemma of weighing patients' physiological status and their feelings of health and well being in their endeavor to attain optimal intervention effectiveness, and patient satisfaction.

Also, in formation on the relationship between measures of disease activity and health-related quality of life may improve communication and compliance with treatment recommendations.

Summary of Literature

SLE is a potentially life threatening disease which, due to its varied and complex manifestations, has had an important impact on society. In order to understand the disease processes of this disorder it is becoming increasingly important to measure outcomes. Three constructs, disease activity, disease damage, and health-related quality of life collectively should reflect the consequences of this disease. Although the survival rate of SLE patients has significantly improved over recent decades, there was not accompanied by an improvement in quality of life these patients. Relative few studies have focused on HRQL in relation to SLE and consequently little is known about the relationships between disease activity, disease damage, and HRQL. Three Canadian studies (Hanly, 1997; Gladman et al., 1996; Gladman et al., 1996) did not find an association with disease

activity or damage and HRQL as measured by the SF-20 (a shorter version of the well-known SF-36). However, one Swedish study (Bombardier et al.,1992) found that disease activity and psychological distress was associated with HRQL among persons with SLE. In the UK, Stoll et al (Stoll et al.,1997) also demonstrated that disease activity was associated with HRQL. In the most recent study, Fortin et al (Fortin et al.,1998) have shown how disease activity and cumulative damage only measure a small part of the overall picture in lupus and suggest that one needs to study the effects of low-grade lupus activity on overall health status. They also identified that an increase in the level of disease activity over time negatively correlated with quality of life.

Although the importance of measuring HRQL in SLE patients is now established, the broader scope of a global measure could potentially capture features not represented by specific indices of HRQL and provide additional information about the relationships between activity, damage and HRQL.

CHAPTER 3

OBJECTIVE

The objective of this study was to estimate the relationship between HRQL and measures of disease activity, disease damage, impairments, disabilities and handicap for persons with SLE..

In order to evaluate whether patient's different levels of disease activity are reflected in their HRQL, a study was initiated in the fall of 1997. The following chapters describe the methods, results, and conclusions of that research project.

CHAPTER 4

The Relationship between Health Related Quality of Life and Disease Activity and Damage among Persons with SLE

Chenchen Wang MD; Nancy E. Mayo, PhD; Paul R. Fortin MD., MPH

Department of Epidemiology and Biostatistics, Faculty of Medicine, McGill University,

Purvis Hall, 1020 Pine Avenue West, Montreal , Quebec, H3A 1A2 Canada

Manuscript prepared for submission to the journal entitled Journal of Rheumatology

Running Title: Quality of life in SLE

In support of this research, Chenchen Wang received a fellowship from the Fonds pour la Formation de Chercheurs et l' Aide â la Recherche FRSQ-FCAR

Communications addressed to

Nancy E. Mayo
Royal Victoria Hospital
Division of clinical Epidemiology
687 Pine Avenue West, Ross 4.29
Montreal, Quebec, H3A 1A1 CANADA
Telephone: (514) 842-1231
Fax: (514) 843-1493
Email: mdnm@musica,mcgill.ca

Introduction

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease of unknown etiology affecting primarily women in their childbearing age. SLE commonly presents with a characteristic butterfly rash of the face, arthritis, fatigue, pleuritic pain, and fever. These reversible symptoms flare and subside and are indicative of disease activity. Prolonged disease activity can lead to irreversible, and potentially lethal, organ damage affecting primarily the kidney and heart (Mills, 1994; Boumpas et al., 1995; Boumpas et al., 1995).

There are a number of measures that have been developed to assess disease activity and damage (Liang et al.,1989; Symmonds et al.,1988; Bombardier et al.,1992; Bombardier et al., 1995; Stoll et al., 1995), however, there are other aspects of the SLE experience, namely the physical, psychological, and social consequences (Naughton et al., 1997), that need to be taken into consideration when evaluating the impact of SLE on the individual. These constructs are captured in health related quality of life (HRQL) measures.

The survival of lupus patients has increased dramatically over the past 20 years (Ginzler,1987; Swaak,1989), so much so that recent studies of outcome in SLE have concentrated on morbidity. The measurement of disease activity and damage are now considered the cornerstones for the assessment of SLE (Decker,1982; Liang et al.,1988). The prolongation of life, however, has not necessarily been translated into good quality of life as many studies have reported poorer HRQL for persons with SLE in comparison to

age- and gender-norms (Fortin et al.,1998; Gladman et al.,1996). The challenge today is to add quality to the duration of life (Fortin et al., 1998). Increasingly, HRQL measures are being included as part of the evaluation of SLE patients, along with the traditional measures of disease activity and damage.

As a consequence of this focus on HRQL, clinical studies about the quality of life of persons with SLE are appearing in the scientific literature (Hanly, 1997; Gladman et al., 1996 (May); Gladman et al., 1996 (June); Burckhardt et al., 1992; Stoll et al., 1997; Fortin et al., 1998; Thumboo et al.,1999). The scientific community has adopted the well-known and perhaps most extensively used generic health related quality of life (HRQL) measure, the Measuring Outcomes Study: Short-Form 36 or 20, as best capturing the consequences of this disease (Stoll et al., 1997).

The current literature indicates that SLE has its most profound impact on aspects of physical health. Gladman et al. (Gladman et al.,1996) and Fortin et al. (Fortin et al.,1998) have shown that persons with SLE have scores for various aspects of physical health that are 30% to 40% lower than age- and gender-peers (Ware, 1994). There was less of an impact on social function. In examining fatigue, Gladman (Gladman et al., 1996) used the Fatigue Severity Scale and noted that SLE patients reported considerably more fatigue than expected (Lauren et al., 1989).

The existing studies of HRQL (Bombardier et al.,1992; Gladman et al.,1996, Gladman et al., 1996; Stoll et al.,1997; Hanley,1997; Fortin et al.,1998) have been inconsistent as to the relationships between disease activity, damage and HRQL. For

example, of four recent Canadian studies, (Gladman et al., 1996; Gladman et al., 1996 Hanley, 1997; Fortin et al., 1998) only one (Fortin et al., 1998) found a relationship (negative) between HRQL and disease activity using the Systemic Lupus Activity Measure (SLAM) while studies using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) does not find any association. Two other studies, one from Sweden using SLAM (Barckhardt et al., 1992) and one from the UK using BILAG (Stoll et al., 1992), also found that HRQL was related to disease activity and psychological distress, however the Swedish study included both persons with lupus and persons with rheumatoid arthritis.

The inconsistent findings suggest that clinical indicators of disease status are not the only factors driving patients perceived health status. Indeed, there are many intervening variables along the path from biological and physiological parameters to health status. According to the World Health Organization's classification of the consequences of disease, the manifestations of disease include impairments, disabilities and handicaps and these are on a continuum that starts with etiological and pathological processes. For any given level of disease activity or damage, there will be a range of functional abilities and for any given functional status there will be a range of values of HRQL. Thus, the variability in HRQL within levels of disease activity is amplified by these intervening variables. This phenomena fits the conceptual model proposed by Wilson and Clearly (Wilson and Clearly, 1995) who suggest that biological and physiological variables impact on HRQL through symptoms (impairments) and function (disabilities). Before a conceptual model for HRQL in lupus can be put forward, it requires testing. This study

was designed to evaluate the relationships between different levels of the WHO model of impairment, disability and handicap as it relates to lupus. The specific objective was to estimate the relationship between HRQL and measures of disease activity, disease damage, impairments, disabilities and handicap for persons with SLE.

METHODS

Study Design and Population

This cross-sectional study included consecutive patients from the Lupus Clinic of Montreal General Hospital, Montreal, Canada. Fifty-four adults (> 18 years of age) who were attending for one of their regular clinic visits between January and May 1998 were enrolled. SLE was defined by the presence of four or more of the revised diagnostic criteria of the American College of Rheumatology (formally the American Rheumatology Association ARA) (Tan et al., 1982; Hochberg, 1997).

Procedure

The patient list for each clinic visit was reviewed by the principal investigator (C.W.) and the clinic nurse to identify eligible patients (see appendix D). While waiting for the clinical appointment, eligible persons were given a package containing documents explaining the study, a consent form and the self-administered questionnaires. Participants were asked to complete a battery of questionnaires, which included one on socio-demographic information, a general assessment of their lupus disease activity (scored on a

10 cm visual analogue scale: VAS); a Medical Outcomes Study Short-Form 36 (SF-36) Health Survey, as well as EuroQol EQ-5D instrument. These questionnaires could be filled out at the visit or taken home to be returned later by mail. Only one person of 55 participates refused the study and all questionnaires were returned.

Participants also underwent a medical examination by their treating physician which served to obtain a standard index of disease activity (SLAM-2, SLEDAI), global assessment of patient's disease activity on a 10 cm VAS; and disease damage (SLICC/ACR DI). Two physicians working regularly at the Montreal General Hospital Lupus Clinic saw the patients. They filled in the different lupus activity measures without knowledge of the results of the laboratory tests immediately after the clinic visit. Laboratory test results were added to the SLAM-2 and SLEDAI by the principal investigator. The study protocol was approved by the participating hospital ethics committees.

All of the data and results including the laboratory tests were part of the routine assessment; the data pertaining to these tests were then added to the existing patient database.

Instrumentation

HRQL was measured by Medical Outcomes Study 36-item Short-Form health survey (SF-36) (Ware and Sherbourne, 1992) and the Euroqol (EQ-5D) (The EuroQol group, 1990; Kind, 1995). The SF-36 was constructed to provide a comprehensive

assessment of the physical and mental components of health status (McHorney et al.,1993; McHorney et al.,1994). The questionnaire measures eight parameters of health status: 1) Physical functioning; 2) Role physical; 3) Bodily pain; 4) General health perceptions; 5) Vitality; 6) Social function; 7) Role Emotional; and 8) Mental health. Scores for each scale range from 0 to 100, with higher scores reflecting better health status.

In addition to the eight scales providing the health profile of the individual, two summary measures (Ware et al., 1994a) are used: physical health measure (PCS) and mental health measure (MCS). These have been standardized to have a mean of 50 and a standard deviation of 10. Higher scores on the scales indicate better health-related quality of life (Ware et al., 1994b).

The Euroqol (EQ-5D) (The EqroQol Group, 1990; Kind, 1996) is also a generic measure which describes health states in terms of five dimensions: mobility (disability), self-care (disability), usual activities (handicap), pain/discomfort (impairment), anxiety/depression (impairment). Each of the dimensions is divided into three levels which when taken together define a total of 243 (3^5) unique health states. Country-specific weights for each of the health states yield a single valuation on a 0 to 1 scale; Canadian weights are not yet available. However, there is also a visual analogue thermometer rating scale to evaluate the overall perception of health on a 0 to 100 scale. The simplicity of this instrument and the fact that the 5 items span impairment, disability and handicap makes it ideal for use in conditions characterized by these consequences (Mayo, 1999). It has been tested in a culturally diverse and bi-lingual Canadian environment and evidence of

construct validity has been found (Mayo, 1999).

Disease activity was assessed using the revised Systemic Lupus Activity Measure (SLAM) (Liang et al.,1989) a validated and reliable instrument, based on physician examination and a laboratory assessment. It reports on lupus activity in nine organs or systems with one additional laboratory category: constitutional (range of scores: 0-8), integumental (0-9), eye (0-9), reticuloendothelial (0-4), pulmonary (0-3), cardiocascular (0-7), gastrointestinal (0-3), neuromotor (0-14), joints (0-3) and laboratory (0-21). The revised SLAM-2 score ranges from 0 (no activity) to 81 (maximum activity). A score over 7 is considered clinically important (moderate to severe clinical activity) as a majority of physicians would consider a change in treatment (initiation or increase in corticosteroids) (Abrahamowicz et al.,1998; Fortin et al., 1998).

A second measure, the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) uses a weighting system to evaluate disease activity in nine organ systems (Bombardier et al., 1992): a weight of 8 is given for each disease activity items in the central nervous system, 4 each for the vascular and renal system items, 2 each for musculoskeletal, serosal, dermal, and immunologic systems, and 1 for constitutional and hematoloic items. The total SLEDAI score can range from 0 (no activity) to 105 (maximum activity). A score of 6 is considered clinically important since it impacts on treatment decisions (Abrahamowicz et al., 1998).

Disease damage was measured using the Systemic Lupus International

Cooperating Clinics/American College of Rheumatology Damage index (SLICC/ACR DI): The SLICC/ACR DI (Gladman et al., 1992; Gladman et al., 1996). This is a physician-rate index, which assesses cumulative organ damage due to either the disease, complications of therapy, or intercurrent illness such as surgery or cancer. It reports on 12 organs or systems which are ocular (range of scores: 0-2), neuropsychiatric (0-6), renal (0-3), pulmonary (0-5), cardiovascular (0-6), musculoskeletal (0-6), dermatological (0-3), gondola (0-1), diabetes (0-1) and malignancy (0-2). Damage in each system must be present for 6 consecutive months in order to be scored. The total SLICC/ACR DI score can range from 0 (no damage) to 46 (maximum damage) but will in fact rarely exceed 10 (24 25) (Gladman et al., 1996).

Statistical Analysis

Basic descriptive statistics were carried out to describe the study population and to examine relationships among study variables. To estimate the relationship between HRQL and measures of disease activity, disease damage, impairments, disabilities and handicaps multiple linear regression was used. Separate models were developed for each outcome measure of HRQL. The SF-36 has 8 separate scales and two component summary scales, Physical Health and Mental Health; the EQ-5D has one value derived from the thermometer rating scale. For each model, the predictor variables were (1) socio-demographic characteristics; (2) clinical measures of disease activity and damage; (3) physicians' and patients' ratings of disease activity; (4) patients report of impairment

(pain/discomfort and anxiety/depression), disability (capacity for mobility and self-care) and handicap (participation in usual activities).

Because age and duration of disease were correlated, they could not be in model at the same time. We chose to use duration of disease as the predictor because it is more clinically relevant in term of disease progression. There were only three men and so gender was not able to be evaluated. We also considered race, occupation, education and marital status.

The clinical variables scores were SLAM, SLEDAI, SLICC, VAS physician and patient and medication use. The measures of impairment, disability and handicap were from the dimensions of the EQ-5D dichotomised into "with problem" or "no problem".

A multiple linear regression model was built for each of the 3 main outcomes: EQ-5D thermometer rating scale, SF-36 Physical Health and SF-36 Mental Health. The Akaike Information Criteria (AIC) was used to select the final model. The best model is that which has the lowest AIC which arises when the error term (SSE) of the model is the smallest. However, the AIC imposes a penalty for the number of independent variables ($AIC = n*\ln(SSE/n) + 2*k$) where n is the sample size and k is the number of independent variables). Residual plots were produced for all non-dichotomous variables and the assumptions for linear regression analysis were checked by visual inspection. Finally, to understand the relationships between disease activity and damage and variables at other levels of the conceptual model for HRQL in lupus, we examined predictors of impairment (pain/discomfort and anxiety/depression), disability (mobility and self-care) and handicap

(usual activities). Because these were dichotomized, logistic regression was used. Logistic regression estimates the probability of a particular outcome as an exponential function of the predictor variables. The regression parameters are interpreted as odds ratios with ninety-five percent confidence intervals (95% CI). The odds ratio approximates the risk ratio (RR) when the outcome is rare (Kleinbaum, 1994). In this study, the outcomes were not rare and therefore OR differs from the RR. As these outcomes are theoretically hierarchical in nature, handicap would not be a predictor of a disability or impairment outcome etc. The predictive models for each outcome are illustrated in Figure 1(see Figure 1). As all the predictor variables are measured on different scales, it is difficult to appreciate the magnitude of the impact of one measure in comparison to the other. To over come this, we used standardized regression co-efficients. These are interpreted in terms of standard deviation units, for every 1 SD change in an "x" variable the "y" variable changes the value of the co-efficient. The SD's were expressed in integers and were derived from the data and verified against other published values (see Appendix F).

RESULTS

Description of the Study Population

Of the 54 patients, the majority were white (n=45), 4 were black, 3 Asian, and 2 of mixed racial origin. The average age of participants was 40 years (range 24-80); there were only three men. Mean disease duration was 13 year (range 1-39). There was a wide range of disease duration (referring to the time since first physician diagnosis), 1 to 39

years; median 11.5 years.

Table 4.1 summarises the clinical characteristics of study participants. The subjects were in the low to moderate disease activity range (SLAM-2: mean 6.3, range 0 to 18; SLEDAI: mean 5.0; range 0 to 26). The physicians and patients' ratings also indicated low disease activity with values ranging from 0 to 5.5 for physician's ratings (mean 1.7) and 0 to 7.3 for patients (mean 3.2).

Physicians' subjective ratings of disease activity were correlated with clinical indices of disease activity. Patient's ratings, however, were lower. There was no correlation between patients' ratings and the SLEDAI which is an index derived largely from clinical and laboratory findings. This is in contrast to the findings of a modest correlation with the SLAM-2, which requires more patients input into the evaluation. These correlations are shown in Table 4.2.

The SLICC/ACR DI indicated that this sample of SLE patients had relatively low disease damage (mean 1.8: SD 2.8); in fact only one person had a score higher than 3 (score of 17).

The scores for the eight SF-36 scales and the two summary scales (Physical Health and Mental Health) are also presented in Table 4.1. Physical Health was on average 38.6 (SD 10.9) and mental health 43.1 (SD 12.3). An examination of the scale scores indicates that this sample of persons with SLE had the greatest difficult in meeting role demands because of physical health (Role-physical: mean 41.7; SD 44.5). The highest score was achieved for Social function (mean 67.8; SD 20.9).

Overall HRQL evaluated using the EQ-5D thermometer VAS was 68.0 (SD=21.0). The number and proportion of persons reporting problems in the dimensions of the EQ-5D are also presented. The most frequent problem was pain, reported by 69% of the sample, and followed by anxiety/depression reported by 46%. Difficulty with usual activities was also prevalent (46% of sample); fewer people reported difficulty with walking (24%) or self-care (13%).

Multivariate Associations

The first set of regression analyses examined factors related to the three principle outcomes: the EQ-5D thermometer VAS and the two SF-36 summary scales. The best models for these analyses are given in Table 4.3. Associated with the EQ-5D were the SLEDAI, a measure of disease activity, and reported difficulty with usual activity, a measure of handicap. For Physical Health, the associated variables were the SLICC, patient rating of disease activity (VAS), difficulty with walking and difficulty with usual activity. These variables represent the constructs of disease damage, disease activity, disability and handicap, respectively. Only anxiety was associated with Mental Health. The proportion of variability explained ranged from 0.46 to 0.59. The parameter estimates associated with the significant model variables indicate the magnitude and direction of the relationship. For example, for every one SD change ($\approx$ 6 units), in the SLEDAI, the EQ-5D thermometer VAS decreased by 5.28 units (adjusted for usual activity).

As usual activity was scored as a dichotomy, the regression parameter indicates that, compared to people with no problem (scored 0), people with difficulty (scored 1) reported their health to be 21 points lower (adjusted for SLEDAI score). For Physical Health, the impact of usual activity was to decrease it by 7.13 units (adjusted for all other model variables). Physical Health has been standardized to have a mean of 50 in a healthy population and the EQ-5D has a mean of about 90 in a healthy population (Mayo, 1999). The standard errors were used to calculate 95% CI's, none of which included the null value of 0.

Subsequent analyses examined associations with each of the SF-36 subscales. The results of the multiple linear regression models are shown in Table 4.4. There were very few common predictors of the 11 indices used to measure aspects of HRQL from among the variables measuring disease activity and disease damage. The SLAM-2 was associated only with general health, the SLEDAI only with EQ-5D VAS. The SLICC (disease damage) was associated with three of the HRQL indices: Physical Health, Physical functioning which is a component of Physical health, and to a lesser extent with Social functioning. Patients' and physicians' ratings of disease activity related to different constructs.

There was a more consistent pattern as to how measures of impairment, disability and handicap related the HRQL (see Table 4.5). The predominance of difficulty with usual activity is noted. Anxiety/depression was mainly associated with indices capturing constructs related to mental health.

Other models were developed to examine relationships between variables on the pathway from disease to HRQL. These intermediate variables are handicap, disability and impairment. Logistic regression was used to identify variables associated with these outcomes. First, variables distinguishing between persons with and without difficulty with usual activity (handicap) were identified. Potential predictors were measures of disease activity and damage, impairment and disability. Both impairment (pain/discomfort and anxiety/depression) and disability (mobility) variables were significant predictors (see Table 4.6). The OR for pain/discomfort adjusted for anxiety/depression and mobility was 11.4. The unadjusted OR is also presented; it is 12.3 which is much higher than the unadjusted risk ratio 5.3, illustrating the non-comparability of the OR and the RR when the outcome is not rare.

Table 4.7 presents predictors of mobility; potential predictors were disease activity and damage and impairment. Only pain/discomfort (impairment), and duration of disease were significant predictors. For pain/discomfort (a measure of impairment), only the patient's perception of disease activity was a significant predictor. The regression coefficient is presented in terms of SD units and indicates that 1 SD change (2 units) in this measure was associated with an increase an OR for having pain of 1.1. No predictors of anxiety/depression were significant.

DISCUSSION

The HRQL of persons with SLE was described here along with its predictors. Two instruments were used for the measurement of HRQL, the very well known SF-36 and the lesser known EQ-5D. Thus, three values for different aspects of HRQL (SF-36: Physical Health & Mental Health and EQ-5D VAS) were generated. As expected, Physical Health and Mental Health were not correlated. The EQ-5D VAS was highly correlated with Physical Health (r=0.66) and modestly correlated with Mental Health (r=0.3).

The Physical Health (SF-36) of the persons with SLE was low (mean 38.6; SD 10.9) in comparison to age predicted norms (mean for women aged 35-44 years: 51.4; SD 10); Mental Health was also lower, 43.1 for SLE vs. 48.8 for population norms (Ware, 1994). For the EQ-5D, the mean thermometer rating VAS was 68 (SD 21), lower than the 82.4 (SD 13.1) derived from a normative population from Montreal, Canada (Mayo, 1999), but higher than that reported from a large sample (n=133) of persons with rheumatoid arthritis (mean 56.4) (Hurst et al., 1997).

Other studies in SLE have used the SF-36 but reporting data for the eight subscales only. Our findings that scores on the subscales were 30% to 40% lower than norms, concur with those of Gladman et al. (Gladman et al., 1996) and Fortin et al. (Fortin

et al., 1998). The areas of HRQL most impacted upon by SLE were Role Physical, General Health, Vitality, and Role Emotional (see Table 4.1).

The use of the EQ-5D was a unique feature of this study. This relatively simple instrument is attractive for use in this population because it captures aspects of health status that relate to the WHO's classification of impairment, disability and handicap (IDH) as consequences of disease. With the inclusion of this instrument, it was possible to make links between disease activity and damage, consequences of disease in terms of IDH and HRQL.

Not surprisingly, the predictors of these three measures differed. Usual activity was a predictor of both Physical Health and the EQ-5D VAS. The only other predictor of the EQ-5D VAS was the SLEDAI, a measure of disease activity. Disease damage, patient's perception of disease activity, and mobility were the other predictors of Physical Health. This would suggest that these two measures of HRQL (Physical Health and EQ-5D VAS) are capturing slightly different constructs with the EQ-5D being mainly influenced by restriction of activity and the SF-36, Physical Health component, being influenced by a wider variety of constructs, reflecting the multi-dimensional content of this instrument.

Not surprisingly, our model revealed that scores registered on SLICC, a measure of damage, were highly predictive of both overall Physical Health and the Physical Function subscale of SF-36. Our findings are similar to those of Fortin (Fortin et al., 1998) where cumulative damage scores were found to affect Physical Function, General Health

and Social Functioning. It is tempting to postulate that once irreversible damage has occurred, it's impact will have a continued effect on physical function, however, other domains such as mental health, or role-emotional may adapt in the presence of damage and not be so affected.

The single item question from the EQ-5D on anxiety/depression was the only predictor of Mental Health component of the SF-36, indicating the congruence of these two measures. This study did not include any other measures of the psychosocial impact of SLE. However, other researchers have pointed out the importance of psychological distress and the patient's perception of the gravity of the illness to the outcome of SLE. (Dobkin et al.,1998; Wekking, 1993).

Like many others (Wekking, 1993; Muldoon, 1998; Dutis et al., 1997; Fortin et al., 1995), we did not find a strong association between patients' and physicians' VAS ratings for disease activity ($r = 0.28$). However, the patients' VAS rating was a predictor of overall Physical Health, two of the SF-36 subscales relating to physical function and role, and presence of pain or discomfort. This suggests that patients rated their disease activity based on physical manifestations of the disease. The physician's VAS rating was highly correlated with the SLAM and SLEDAI, two measures of disease activity as evaluated by the physician, indicating that these three measures are capturing the same construct.

A key finding from this study was the relationship among variables that are related to HRQL. The analyses carried out here permitted the formulation of an empirical model

for HRQL as it applies to SLE. This model is presented in Figure 1. The main feature is the hierarchical relationship between impairment, disability and handicap with HRQL. However, the influences of disease parameters, as measured by standard scales as well as patients' perceptions, are non negligible. This model is similar to that proposed by Wilson and Cleary (Wilson and Cleary, 1995) although only a limited number of constructs were considered here.

One potential limitation of this study was its cross-sectional nature. However, SLE is a chronic disease of long duration characterized by periods of exacerbation and remission. During remission, patients feel generally well and during an exacerbation they can be acutely ill. Thus, findings from a longitudinal study, that missed periods of exacerbation, would not differ greatly from those generated from a cross-sectional study. However, it is difficult to conclude a causal relationship in a cross-sectional study when there is doubt about the timing of the relationships. In SLE, it would be difficult to imagine that poor HRQL contributed to disease activity and not visa versa.

The major limitation is in the variety of constructs measured. Here, we focused on measures of disease activity and damage and included, in a limited fashion, measures of impairment, disability and handicap. These latter measures could be expanded to include performance based measures of physical function and community activity. It would also have been interesting to include measures of psychological distress, self-efficacy and self esteem. However, it would be burdensome for patients to complete such a large battery of tests at any one time. There is no disease specific measure of HRQL for SLE and so

we relied on a generic measure which may not be detailed enough to characterize fully the impact of SLE (Kaze et al.,1992; Liang et al., 1985). Several important domains for SLE are not captured in generic measures, specifically, sexual activity, sleep, and family function. Finally, the study sample was small particularly for finding relationships between variables measured on a dichotomous scale. The study was powered to find associations between pairs of variables in the order of 0.5.

One of the criticisms of HRQL measures is that they measure constructs outside of the realm of the clinician. For HRQL measures to be used in clinical decision making, they must be shown to add value to the clinician's understanding of the way an individual is affected by his or her disease, over an above the usual clinical measurements (Lydick, 1998). To appreciate the added value of measuring HRQL, the amount of variability in the three measures of HRQL explained by usual clinical assessments was calculated. The only clinical measures related to Physical Health, were the SLICC and the patient's VAS; together these two measures explained 38% of the variability in Physical Health. Difficulty with mobility and with carrying usual activities, together with these two clinical measures accounted for 59% of variability (see Table 4.3). For the EQ-5D VAS, the SLEDAI was the only associated clinical measures accounting for only 9% of variability. However, adding difficulty with usual activity accounted for 46% of variability. No clinical measure explained mental health (see Table 4.3).

No one would doubt the value of how the patient feels, in fact this is usually the first question asked in any clinical encounter. "How are you?" can be thought of as a

global quality of life question (Lydick and Yawn, 1998). Clinical measures of SLE disease activity and damage accounted for only a tiny proportion of how a patient feels. This would support incorporating standardized measures into routine clinical practice in order to appreciate more fully the impact of this disease on the individual.

AKNOWLEGMENTS

The authors wish to thank research nurses Ms. Carolyn Neville, Diana Ferland, Dr. Ann Clarke and Claudette Corrigan for her assistance in running the study.

References

Abrahamowicz M et al (1998): The relationship between disease activity and physician's decision to start treatment in active systemic lupus erythematosus. J Rheumatol 25: 277-284.

Bombardier C, Gladman DD. Chang CH, Urowitz MB, and the Committee on Prognosis Study in SLE (1992): Development of the disease activity index: the SLEDAI. Arthritis Rheum 35: 630-40.

Boumpas DT, Austin HA, Fessler BJ, Balow JE, Klippel JH, Lockshin MD (1995): Systemic lupus erythematosus: emerging concepts. Part I: renal, neuropsychiatric cardiovascular, pulmonary, and hematological disease. Ann Intern Med 122:940- 950.

Boumpas DT, Fessler BJ, Austin HA. Balow JE, Klippel JH, Lockshin M D (1995): Systemic lupus erythematosus: emerging concepts. Part 2: dermatologic and joint disease, the antiphospholipid antibody syndrome, pregnancy and hormonal therapy, morbidity and mortality, and pathogenesis. Ann Intern Med 123: 42-53.

Burckhardt CS, Archenholtz B. Bjelle A (1992): Measuring the quality of life of women with rheumatoid arthritis or systemic lupus erythematosus: a Swedish version of the Quality of Life Scale. J. Rheumatol 21(4): 190-5.

Decker JL (1982): The management of systemic lupus erythematosus. Arthritis Rheum 25: 891-894.

Dobkin PL et al (1998): Psychosocial contributors to mental and physical health in patients with systemic lupus erythmatosus. Arthritis Care and Research 1:23-31.

Dutis AA, Boeke S, Taams MA, Passchier J, Erdman RA (1997): Prediction of quality of life after coronary artery bypass graft surgery: A review and evaluation of multiple, recent studies. Psychosomatic Medicine 59: 257-268.

Fortin PR, Abrahamowicz M, and Danoff D (1995): Small changes in outpatient lupus activity are better detected by clinical instruments than by laboratory tests. J Rheumatol 22: 2078-83.

Fortin PR et al (1998): Impact of disease activity and cumulative damage on the health of lupus patients. Lupus 7: 101-107.

Ginzler EM. Berg A(1987): Mortality in systemic lupus erythmatosus. .J Rheumatol (suppl 13) 14:218-22.

Gladman D, Ginzler E, Goldsmith C, et al (1992): Systemic lupus international collaborative clinics: Development of a damage index in systemic lupus erythematosus. J Rheumatol 19: 1820-1.

Gladman DD et al (1996): Lack of correlation among the 3 outcomes describing SLE: disease activity, damage and quality of life. Clinical & Experimental Rheumatology. 14 (3): 305-8

Gladman D, Urowitz M, Ong A, Gough J(1996): A comparison of 5-health status instruments in patients with systemic lupus erythmatosus (SLE). Lupus 5:190-5

Gladman, D et al (1996): SLE workshop report. Systemic lupus international collaborating clinics conference on assessment of lupus flare and quality of life measures in SLE. San Francisco, USA, J Rheumatol 23: 1953-1955.

Gladman D. Urowitz M. et al (1996): Systemic Lupus International Collaborating Clinics conference on assessment of lupus flare and quality of life measures in SLE. Systemic Lupus International Collaborating Clinics Group. J Rheumatol 23(11): 1953-5.

Gladman D, Ginzler E, Goldsmith C, et al (1996): The development and initial validation of the SLICC/ ACR damage index for SLE. Arthritis Rheum 39: 363-9.

Hanly JG (1997): Disease activity, cumulative damage and quality of life in systemic lupus erythematosus: results of a cross-sectional study. Lupus 6(3): 243-7.

Hochberg MC (1997): Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus (letter). Arthritis Rheum. 40 (9): 1725.

Hurst NP, Kind P, Ruta DA, Hunter M, Stubbings A (1997): Measuring health-related quality of life in rheumatoid arthritis: validity, Responsiveness and reliability of EuroQol (EQ-5D). BR J Rheumatol 36: 551-9.

Katz ME, Harris WJ, Levitsky K et al (1992): Methods for assessing condition-specific and generic functional status outcomes after total knee replacement. Med Care 30:240

Kind P (1995): The EuroQol Instrument: An Index of Health-Related Quality of Life. In: Spilker B, editor. Quality of Life and Pharmacoeconomics in Clinical Trials. Second Philadelphia: Lippincott-Raven Publishers 191-201.

Kleinbaum DG, Kupper LL, Morgenstern H (1982): Epidemiologic Research: Principles and Quantitative Methods. Life Learning Publications, Belmont, California.

Krupp LB et al., (1989): The fatigue severity scales application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 46: 1121-1123.

Liang MH, Socher SA, Roberts WN, Esdaile JM (1988): Measurement of systemic lupus erythematosus activity in clinical research. Arthritis Rheum 31: 817-825.

Liang MH, Socher SA, Larsen MG, Schur PH (1989): Reliability and validity of six systems for the clinical assessment of disease activity in SLE. Arthritis Rheum 32: 1107-18.

Liang MH, Larson MG, Cullen KE, Schwartz J A (1985): Comparative measurement efficiency and sensitivity of live health status instruments for arthritis research. Arthritis Rheum 28: 542.

Lydick E, Yawn BP (1998): Clinical interpretation of health-related quality of life data. Quality of life assessment in clinical trials: Methods and practice. New York: Oxford University Press.

Mayo EN,Goldberg M, Kind P (1998): Performance of the Euroqol EQ-5D in a Canadian population. Proceedings of the EuroQol Plenary Meeting

Mills JA (1994): Systemic lupus erythematosus. N Engl J Med 330: 1871-9.

McHorney C, Ware JE, Raczek A (1993): The MOS 36-item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 31: 247-63.

McHorney C, Ware JE, Lu J, Sherbourne C (1994): The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care 32: 40-66.

Muldoon MF, Barger SD, Flory JD, Manuck SB (1998): What are quality of life measurements measuring? BMJ 316: 542-545.

Naughton MJ, Shumaker SA (1997): Assessment of health-related quality of life in orthopaedic outcomes' studies. J Arthroscopic and Related Surgery 13 (1) 107-113.

Stoll T, Gordon C, Seifert B et al (1997): Consistency and validity of patient administered assessment of quality of life by the MOS SF-36; its association with disease activity and damage in patients with systemic lupus erythematosus. J Rheumatol 24 (8): 1608-1614.

Stoll T, Seifert B, Isenberg DA (1996): ACR/SLICC Damage Index is a useful predictor of severe outcome in SLE patients and an indicator of morbidity in different ethnic groups. Br J Rheumatol 35: 248-54.

Symmons DPM, Coppock JS, Bacon PA et al (1988): Development and assessment of a computerized index of clinical disease activity in systemic lupus erythematosus. Quart J Med 69: 927-37.

Swaak AJG, Nossent JC, Smeenk RJT (1991): Prognostic factors in systemic lupus Erythematosus: Rheumatol Int 11:127-132.

Tan EM, Cohen AS, Fries JF, et al (1982): The 1982 revised criteria for the classification of systemic lupus erythemotosus. Arthritis Rheum. 25: 1271-1277.

The EuroQol group (1990): EuroQol A new facility for the measurement of health related quality of life. Health Policy 16 199-208.

Thumboo J et al (1999): Validation of the MOS SF-36 for quality of life assessment of patients with systemic lupus erythematosus in Singapore. J Rheumatol 26: 97-102.

Urowitz MB et al (1976). The bimodal mortality pattern of systemic lupus erythmatosus. AM J Med 60: 221-225.

Ware, JE, Kosiniski, M.,& Keller,S.D (1994). SF-36 Physical and Mental Health scales: A user's manual. Boston: The health Institute, New England Medical Center.

Ware JE, Keller S, Bentler PM, Sullivan M, Brazier J, Gandek B (1994a): Comparison of health status measurement models and the validity of SF-36 in Great Britain, Sweden, and the USA. Quality of Life Research 3: 68.

Ware JE, Kosinski M, Keller SD (1994b): SF-36 Physical and Mental Health Summary Scales: A User's Manual. Boston. MA: The Health Institute. New England Medical Center.

Ware, JE, & Sherbourne CD (1992): The MOS 36-Item Short-Form Health Survey SF-36 health status survey. 1. Conceptual framework and item selection. Medical Care 30, 473-483.

Wilson IB, Cleary PD (1995): Linking clinical variables with health-related quality of life: A conceptual model of patient outcomes. JAMA 1:59-65.

Wekking EM (1993): Psychiatric symptoms in Systemic Lupus Erythematosus: An update. Psychosomatic Medicine 55: 219-228.

Table 4.1: Health Profile of Study Participants

Construct (Scoring Range)	Mean (N=54)	SD	Range
Duration of illness (years)	13	8	1-39
Disease Activity			
SLAM-2 (0-93)	6.3	4.1	0-18
SLEDAI (0-105)	5.0	5.8	0-26
MD-VAS (0-10)	1.7	1.4	0-5.5
P - VAS (0-10)	3.2	2.3	0-7.3
Disease Damage			
SLICC (0-43)	1.8	2.8	0-17
Health Related Quality of Life			
Physical Health (0-50)	38.6	10.9	18-57
Mental Health(0-50)	43.1	12.3	14-63
SF-36 Subscales (0-100)			
Physical functioning	64.5	27.3	0-100
Role-Physical	41.7	44.5	0-100
Bodily Pain	53.3	35.2	20-100
General Health	46.9	23.2	5-100
Vitality	46.1	22.7	0-100
Social functioning	67.8	20.9	25-100
Role-Emotional	52.5	46.1	0-100
Mental Health	66.6	19.1	24-100
Health Status (EQ-5D)			
EQ-5D Thermometer Rating Scale (0-100)	68.0	21.0	10-100
	N	**%**	
Mobility, Problem (%)	13	24	0-1
Self-care, Problem (%)	7	13	0-1
Usual Activity, Problem (%)	25	46	0-1
Pain, Problem (%)	37	69	0-1
Anxiety, Problem (%)	25	46	0-1

Abbreviations:
SD: Standard Deviation
MD-VAS: Physician Visual Analogue Scale .
P-VAS: Patient Visual Analogue Scale .
SLAM: Systemic Lupus Activity Measure.
SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.
SLICC: Systemic Lupus International Collaborative Clinics Damage Index.

Table 4.2: Pearson Correlation between Physicians and Patients' Rating of Disease Activity

	SLAM-2	Physician VAS	Patient VAS
SLEDAI	0.45**	0.46**	-0.05
SLAM-2		0.60 **	0.30*
Physician-VAS			0.28 *

** $p<0.001$; * $p<0.05$

Table 4.3: Results of Multiple Linear Regression Identifying Variables Independently Related to HRQL

Health Outcome	Variables	*Parameter Estimate (β)	Standard Error (SE)	95 % Confidence Interval	R^2
EQ-5D Thermometer Rating Scale	SLEDAI	-5.28	2.22	(-9.63, -0.93)	0.46
	Usual Activity	-21.2	3.57	(-28.20,-14.20)	
Physical Health of SF-36	SLICC	-4.65	1.23	(-7.30, -2.00)	0.59
	P-VAS	-0.24	0.12	(-0.48, -0.01)	
	Mobility	-6.06	2.89	(-11.72, -0.40)	
	Usual Activity	-7.13	2.42	(-11.87, -2.39)	
Mental Health of SF-36	Anxiety/ Depression	-15.00	2.66	(-20.21, -9.79)	0.47

Abbreviations:

β is the parameter estimate; SE is the standard error.
P-VAS: Patient Visual Analogue Scale of disease activity.
SLEDAI: Systemic Lupus Erythematosus Disease Activity Index
SLICC: Systemic Lupus International Collaborative Clinics Damage Index
*Per 1SD; SLEDAI 6 units; SLICC 3 units, P-VAS 2 units;

Table 4.4 : Results of Multiple Linear Regression Identifying Variables Independently Related to SF-36 Subscales

Outcome SF-36 Subscales	Variables	*Parameter Estimate (β)	Standard Error (SE)	95 % Confidence Interval	R^2
Physical function	Self-care	-26.40	6.56	(-39.26, -13.54)	0.64
	Usual activity	-17.24	5.56	(-28.14, -6.34)	
	SLICC	-8.64	2.73	(- 15.4, -1.88)	
	P-VAS	-0.52	0.26	(- 1.15, -0.11)	
Role physical	Usual activity	-44.92	7.53	(-59.68, -30.16)	0.47
	P-VAS	-1.62	0.72	(-.2.68, -0.56)	
Bodily pain	Anxiety/depression	-22.47	8.65	(-39.42, -5.52)	0.18
Vitality	Usual activity	-16.35	4.49	(-25.15,-7.55)	0.40
	Anxiety/depression	-12.98	5.04	(-22.86, -3.10)	
Social function	SLICC	-6.57	2.61	(-12.40, -0.78)	0.36
	Anxiety/depression	-14.37	4.61	(-23.41,-5.33)	
	Pain/Discomfort	-9.49	4.10	(-17.53,-1.45)	
Role emotional	Usual activity	-39.17	9.23	(-57.26, -21.09)	0.32
	MD-VAS	-2.22	1.0	(-4.42, -0.02)	
Mental health	Anxiety/depression	-21.67	4.24	(-29.98,-13.36)	0.42
General health	Usual activity	-20.37	4.00	(-28.21,-12.53)	0.50
	SLAM	-11.40	3.54	(-18.34, -4.46)	

Abbreviations:
β is the parameter estimate; SE is the standard error. β/SE is equivalent to a t-test.
P-VAS: Patient Visual Analogue Scale of Disease Activity.
MD-VAS: Physician Visual Analogue Scale of Disease Activity.
SLEDAI: Systemic Lupus Erythematosus Disease Activity Index
SLAM: Systemic Lupus Activity Measure.
SLICC: Systemic Lupus International Collaborative Clinics Damage Index
*Per 1SD; SLAM 6 units; SLICC 3 units, P-VAS 2 units; MD-VAS 2 units.

Table 4.5a: Summary of the Relationship between Disease Activity and Damage with Measures of Health Status

	SLAM	SLEDAI	SLICC	Patient-VAS	Physician-VAS
EQ-5D VAS	-	+	-	-	-
SF-36 Summary Measures:					
Physical Health(PCS)	-	-	++++	+	-
Mental Health (MCS)	-	-	-	-	-
SF-36 Subscale					
Physical functioning(PF)	-	-	+++	+	-
Role Physical (RP)	-	-	-	+	-
Bodily Pain (BP)	-	-	-	-	-
General Health (GH)	++	-	-	-	-
Vitality (VI)	-	-	-	-	-
Social Functioning (SF)	-	-	+	-	-
Role Emotional (RE)	-	-	-	-	+
Mental Health (MH)	-	-	-	-	-

Abbreviations:
SLEDAI: Systemic lupus Erythematosus Disease Activity Index .
SLAM: Systemic Lupus Activity Measure.
SLICC: Systemic Lupus International Collaborative Clinics Damage Index.
Each sign represents the p-value. Statistical significance of results if marked as follows:
+ P<= 0.05 ;++ P<= 0.01; +++ P<=0.001; ++++ P<=0.0001. - no significant relationship.

Table 4.5b: Summary of the Relationship between Impairments, Disabilities and Handicaps with Measures of Health Status

	Usual Activity	Anxiety /Depression	Pain/ Discomfort	Self-care	Mobility
EQ-5D VAS	++++	-	-	-	-
SF-36 Summary Measures:					
Physical Health (PCS)	+++	-	-	-	+
Mental Health (MCS)	-	++++	-	-	-
SF-36 Subscale					
Physical Functioning(PF)	+++	-	-	+++	-
Role Physical (RP)	++++	-	-	-	-
Bodily Pain (BP)	-	+	-	-	-
General Health (GH)	++++	-	-	-	-
Vitality (VI)	+++	+	-	-	-
Social Functioning (SF)	-	++	+	-	-
Role Emotional (RE)	+++	-	-	-	-
Mental Health (MH)	-	++++	-	-	-

Abbreviations:
Each sign represents the p-value. Statistical significance of results if marked as follows:
+ P<= 0.05;++ P<= 0.01; +++ P<=0.001; ++++ P<=0.0001.
- no significant relationship.

Table 4.6: Variables Related to Problem with Usual Activity

Variables	Problem with Usual Activity n = 25	No problem with Usual Activity n =29	Adjusted Odds Ratio* 95% CI	Unadjusted Odds Ratio Risk Ratio 95% CI
Pain/discomfort				
Yes	23	14	11.36	12.32
				2.44, 62.14
No	2	15	1.65, 78.37	
				5.28
				3.69, 6.89
Anxiety/depression				
Yes	17	8	7.91	5.58
				1.73, 17.98
No	8	21	1.75, 35.82	
				2.47
				1.02, 3.92
Mobility				
Yes	11	2	8.90	10.61
				2.06, 54.63
No	14	27	1.45, 54.74	
				2.48
				0.66, 4.30

Table 4.7: Variables Related to Problem with Mobility

Variables	Problem With Mobility n = 13	No problem with Mobility n =41	Adjusted Odds Ratio* 95% CI	Unadjusted Odds Ratio Risk Ratio 95% CI
Pain/discomfort				
Yes	12	25	8.87 1.00, 79.8	7.68 0.91, 64.91
No	1	16		5.52 3.38, 7.66
Duration: mean (SD)	16.8 (8.3)	11.1(7.5)	2.54 1.67, 3.41	

*Per 1SD; Duration 10 years.

Table 4.8: Variables Related to Problem with Pain/Discomfort

Variables	Problem with Pain N =37	No Problem with Pain N =17	Odds Ratio	95% Confidence interval
P-VAS: Mean (SD)	38.36 (22.06)	18.50 (17.54)	1.10	1.03, 1.17

Abbreviations:
P-VAS: Patient Visual Analogue Scale of Disease Activity.
*Per 1SD; P-VAS 2 units.

CHAPTER 5

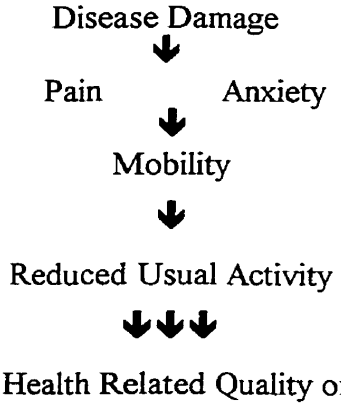
Summary and Conclusions

A growing number of health care researchers have turned their attention to the assessment of how patients experience disease and treatment. Information gained from such inquiry through the medium of patients' self-reports on Health Related Quality of Life (HRQL) questionnaires, is now acknowledged to be an important component in the evaluation of health care. It reflects patients' perceptions of the impact of disease and treatment on the biological, psychological, and social dimensions of their health (Naughton and Shumaker,1997; Guyatt, 1993; Testa and Simonson, 1996). Naughton (Naughton and Shumaker, 1997) suggests that health perceptions are important predictors of health outcomes independent of the patients' clinical health status. This same suggestion has been made in several collaborated rheumatologic studies (Wolfe et al., 1991; Pincus et al., 1987). Standardized self-reported surveys of health not only render sensitive information that is crucial to the success of quality overall health care, they also have the advantages of being easy to administer and inexpensive to process. This philosophy was supported by this study and it was concluded that there would be considerable value added to the therapeutic encounter by including a measure of HRQL as part of the global evaluation of the impact of SLE. However, it is not enough just to collect the information, clinicians must also be trained to interpret the findings and to make appropriate clinical decisions based on all the information gathered (Kosinski, 1997; Burnam, 1997; Nelson, 1997).

Against this background of prior use of HRQL in SLE patients, our cross-sectional study compared the performance of two generic HRQL instruments (SF-36 and EQ-5D) on a consecutive series of 54 lupus patients attending a SLE clinic at a major university teaching hospital in a large metropolitan area. This study contributed to our knowledge about the relationship between disease activity, disease damage, impairments, disabilities, handicaps and HRQL by examining the relationship between these constructs.

A review of the literature and an understanding of the relationship between disease activity and health status related to lupus patients' situation, provided us with a conceptual framework from which were able to orient our analyses of the relationships that are revealed this study. Based on this framework it is possible to propose the following theoretical model for the impact of SLE on the individual.

Theoretical model for the study pattern



This basic conceptual framework was used to choose the variables for the statistical models (see Figure 1). Generally, the results of our study support this theoretical model for HRQL

with a few modifications.

Also, Figure 2 illustrates the relationships that were established from this study. The variables are not as linear as original supposed. However, impairment and disability, impacted on HRQL, only through their relationship with handicap. Characteristics of the patient's disease impacted more widely than expected influencing, impairment (primarily pain), disability (primarily mobility) and HRQL. It would not be unusual for any one with a known disease process that is progressive in nature and potentially life threatening to report lower HRQL even if their actual symptomatology is relatively benign.

Our empirical model is not vastly different from other conceptual models for HRQL. For example, the Wilson and Clearly model (Wilson and Clearly, 1995) (see Figure 3) also shows that there are many intervening variables between disease process and HRQL. In addition, there are a number of modifying factors such as personality, motivation, values, preferences and environmental factors that are potentially important. We did not include such a wide variety of measures, as the response burden would have been too much. We would recommend that future studies, tackle one or two aspects of this complex relationship at a time.

Another model based on the WHO, IDH framework was proposed for rheumatoid arthritis by Fitzpatrick and Badley (Fitzpatrick and Badley, 1996). This model is again linear in nature (see Figure 4) and also depicts the importance of the environment, resources and social setting as interacting factors. This model goes only as far as handicap and does not illustrate the relationship with HRQL.

FIGURE 1 Four Steps used to Test Relationships Among Variables Related to HRQL

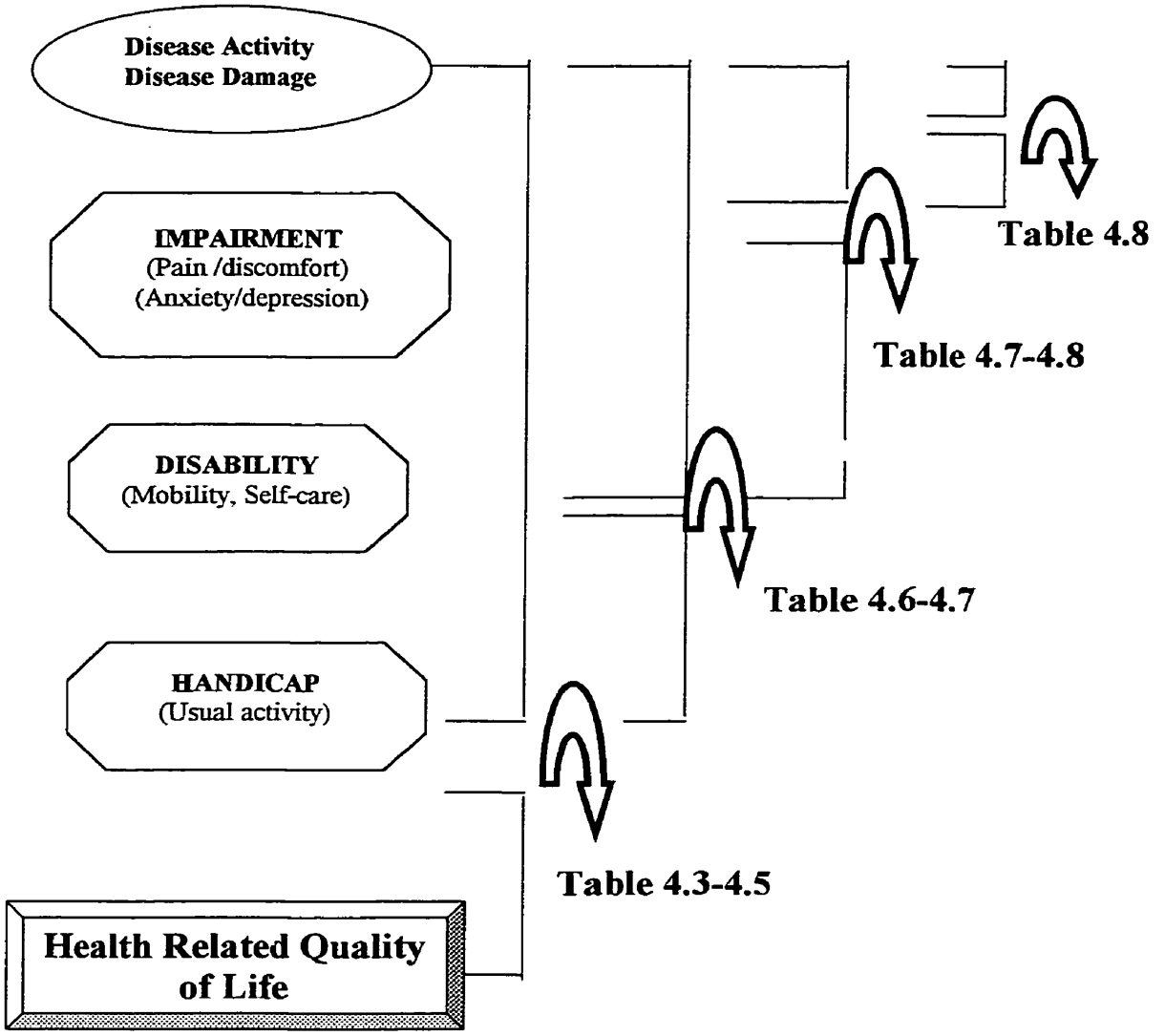


FIGURE 2 Relationships among Variables Related to HRQL

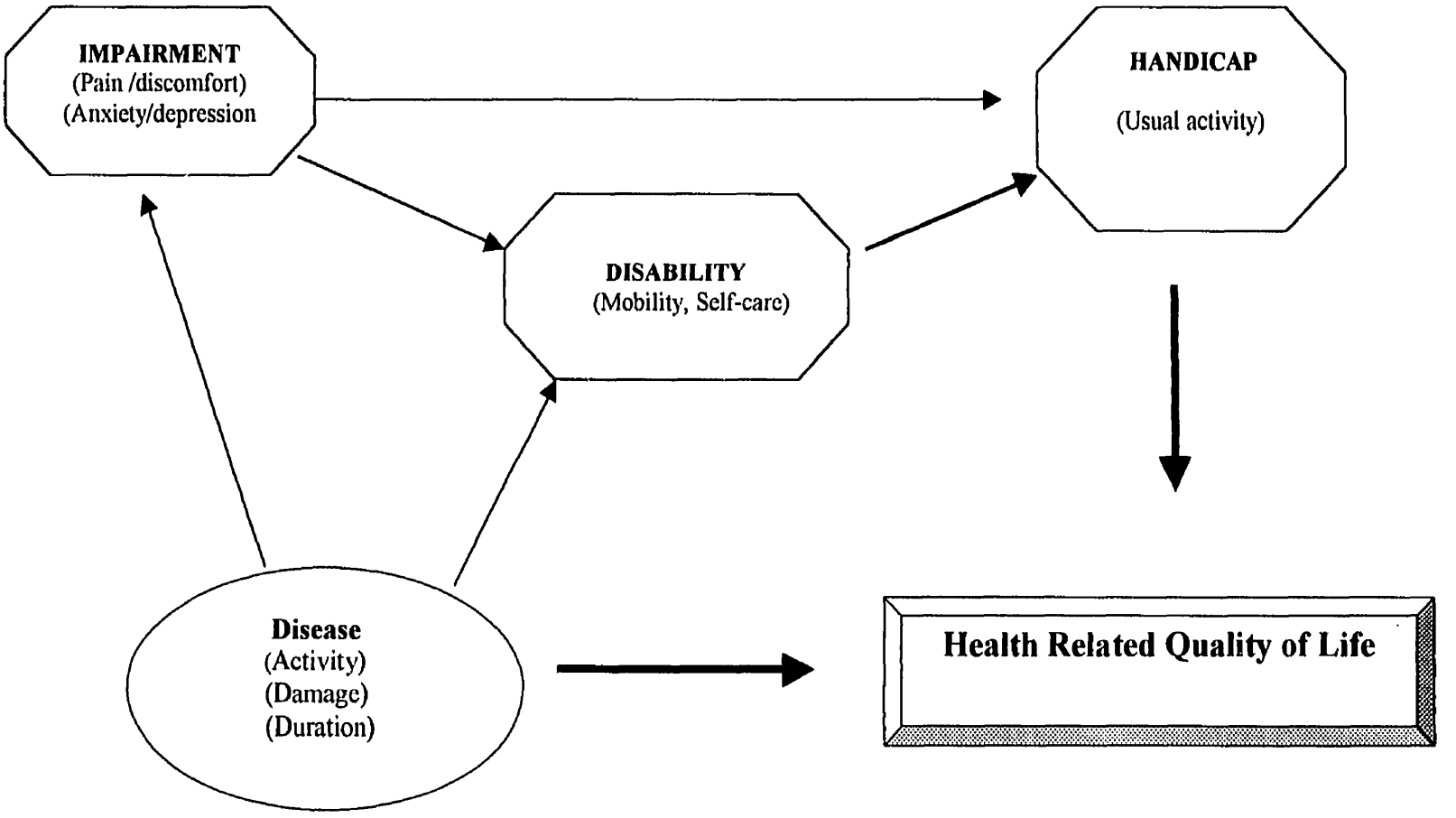


FIGURE 3. Wilson and Cleary's model for health-related quality of life

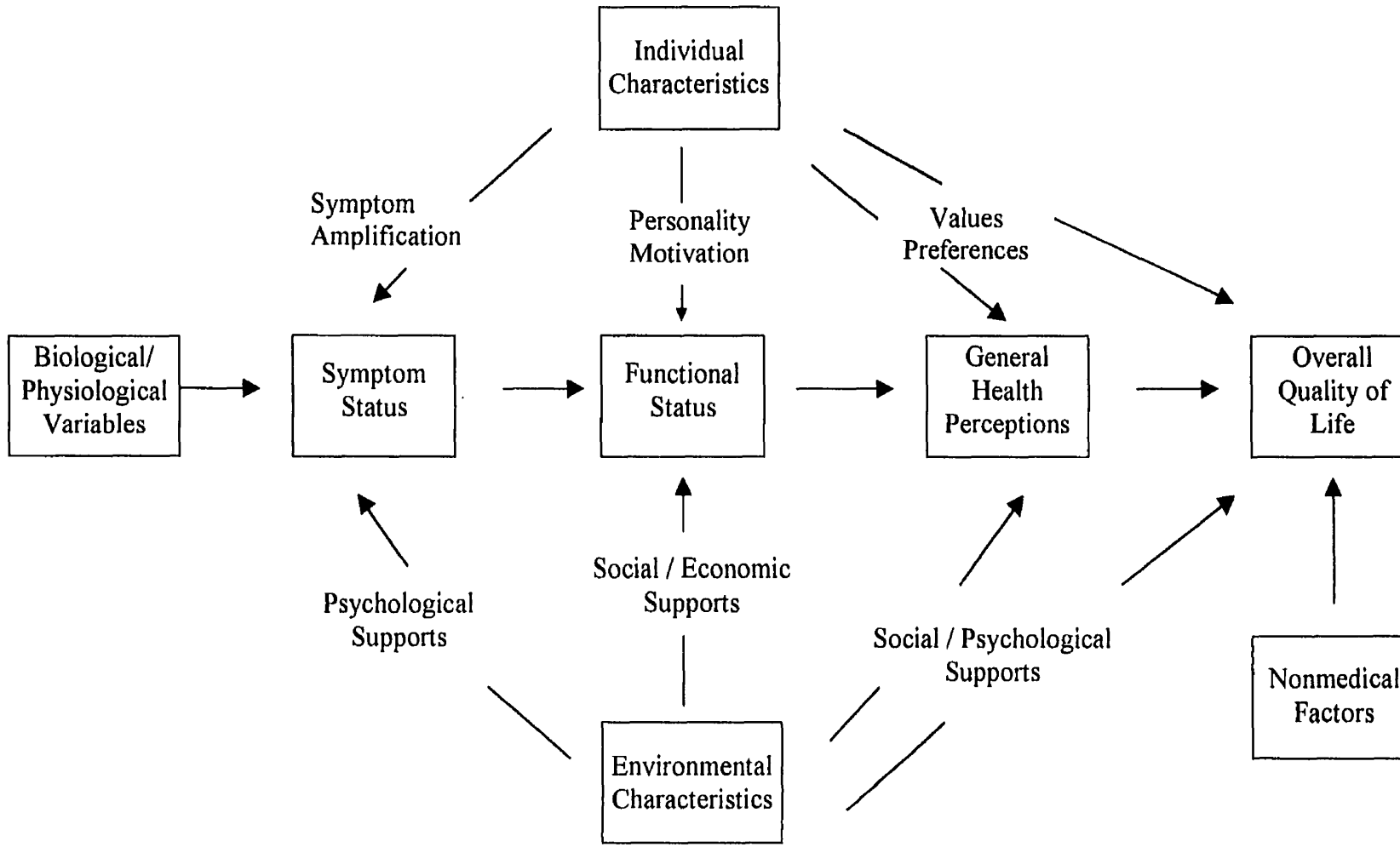
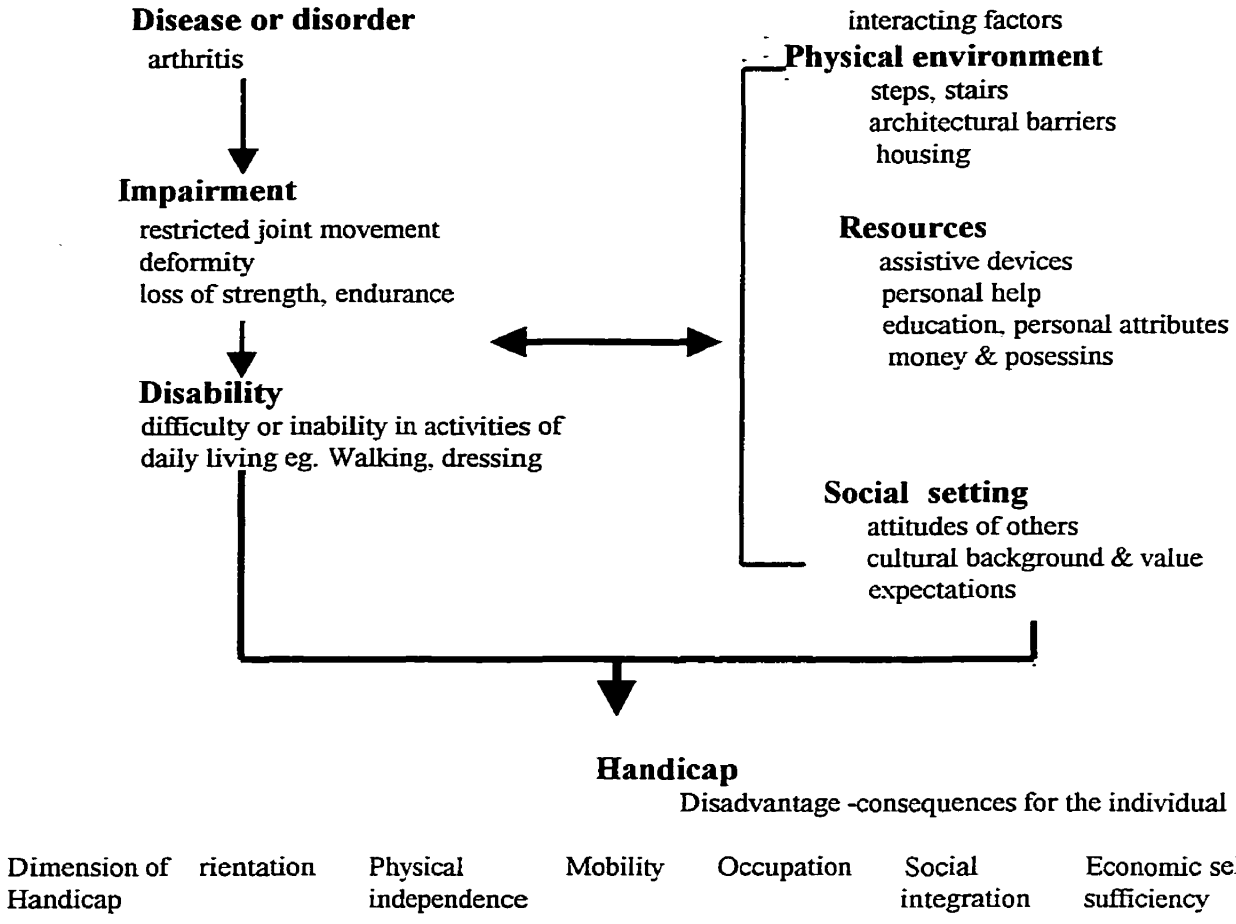


Figure 4 The WHO ICIDH framework for disability assessment in rhematology



Even though it is known that SLE can have a broad effect on patient's HRQL, few general health status instruments have been used to assess these aspects of the impact of this disease on SLE patients. These instruments were designed to be used across a wide spread of patient populations and thus generally believed to be less sensitive, and therefore less useful, than disease-specific measures (Guyatt et al., 1986). In spite of their rather limited prior use in this context, the ability to incorporate information from HRQL

measures into clinical assessment for SLE is now considered desirable in the implementation of a comprehensive and successful over-all health-care plan for SLE patients.

This study has provided evidence to support the idea that there is a significant relationship between cumulative damage, disease activity and lupus patients` perceived health status and has identified the factors contributing to health status. From the above-discussed models, it would appear to be useful to develop a SLE specific HRQL measure. Some findings support that both general health measures and specific clinical measures are necessary to monitor health outcomes (Ware and Sherbourne, 1992). However, the lack of responsiveness of generic measures may pose a problem concerning monitoring change in disease activity over time (Wood-Dauphinee, 1999). Therefore, generic measures may not be useful for a disease such as SLE that has exacerbations and remissions. What important HRQL domains of SLE should be included in such a disease specific measure? When considering the above three theoretical models, it could be suggested to include the following domains: Physical Functioning, including walking, self-care, recreational/leisure time activities, and physical fatigue; Mental Functioning, including anxiety, depression, and vitality; Disease Activity. pain, loss of strength, and Role Functioning, social and occupational activities; Other area could be self-esteem, mastery and self-efficacy.

Therefore, there is no doubt that the evaluation of health outcome in general, should take into account not only the duration of life, but also the degree of quality with

which that life is enjoyed or endured. Further work should be carried out to evaluate more fully the HRQL for persons with SLE and particularly those aspects of HRQL that can be modified through health care interventions and life style choices.

REFER ENCES

Abrahamowicz M et al (1998): The relationship between disease activity and physician's decision to start treatment in active systemic lupus erythematosus. J Rheumatol 25: 277-284.

Abu-Shakra M, Urowitz MB, Gladman DD, et al (1995): Mortality studies in systemic lupus erythematosus: results from a single centre. I: causes of death. J Rheumatol 22: 1259-64.

American College of Rheumatology (1988):" Dictionary of the Rheumatic Diseases, Volume III: Health Status Measurement." Bayport, NY Contact Associates International.

Boumbardieri S et al (1995): Activity criteria in systemic lupus erythematosus. Lupus 4:5

Bombardier C, Dafan D et al (1992): Derivation of the SLEDAI: A disease activity Index for lupus patients. Arthritis and Rheumatism 35 (6): 630-640.

Boumpas DT, Austin HA, Fessler BJ(1995a): Systemic lupus erythematosus: emerging concepts. Part I: renal, neuropsychiatric cardiovascular, pulmonary, and hematological disease. Ann Intern Med 122:940-950.

Boumpas DT, Fessler BJ, Austin HA et al (1995b): Systemic lupus erythematosus: emerging concepts. Part 2: dermatologic and joint disease, the antiphospholipid antibody syndrome, pregnancy and hormonal therapy, morbidity and mortality, and pathogenesis. Ann Intern Med 123: 42-53.

Burckhardt CS, Archenholtz B. Bjelle A (1992): Measuring the quality of life of women with rheumatoid arthritis or systemic lupus erythematosus: a Swedish version of the Quality of Life Scale. J. Rheumatol 21(4):190-5.

Burnam A (1997): Evaluating the outcomes of depression care. Medical Outcomes Trust Bulletin. 1(1): 17.

Cervera R, Khamashta MA et al (1993): Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1,000 patients. Medicine 72:113-24.

Cohen AS, Reynolds WE, Franklin EC, et al (1971): Preliminary criteria for the classification of SLE. Bul Rheum Dis 21: 643.

Cohen AS, Canoso JJ (1972): Criteria for the classification of systemic lupus erythematosus: status 1972. Arthritis Rheum 15: 540-543.

Committee on prognosis studies in SLE (1986): Prognosis studies in SLE: An activity index (abstr). Arthritis Rheum 29: S93.

Carr AJ, Thompson PW, Kirwan JR (1996): Quality of life measures. B J Rheumatol 35 (3): 275-281.

Deyo RA, Andersson G et al (1994): Outcome measures for studying patients with low back pain. Spine 19 (18S): 2032S-2036S.

Deyo RA (1988): Measuring the functional status of patients with low back pain. Arch Phys Med Rehabil 69: 1044-1053.

Decker JL (1982): The management of systemic lupus erythematosus. Arthritis Rheum, 25: 891-894.

Ellen M. Gizler (1990): Clinical feature and complication of SLE, and assessment of disease activity. Current Opinion in Rheumatology 2:730-707.

Esdaile JM (1994): Prognosis of systemic lupus erythematosus. Springer Semin Immunopathol 16:337-355.

Fessel WJ (1974): Systemic lupus erythematosus in the community. Arch Intern Med 134: 1027-1035.

Felson DT, Anderson JJ, Boers M et al.,(1993): The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. Arthritis & Rheumatism. 36 (6):729-740.

Feinstein AR, Josephy BR, Wells CK (1986): Scientific and clinic problems in indexes of functional disability. Ann Intern Med 105: 413-420.

Fitzpatrick F, Badley EM (1996): An overview of disability. B J Rheumatol. 35: 184-187.

Fortin PR, Abrahamowicz M et al (1998): Impact of disease activity, cumulative damage on the health of lupus patients. Lupus 7: 101-107.

Fryback DG, Keeney RL (1983): Constructing a complex judgmental model: an index of trauma severity. Manage Sci 29: 869-883.

Ginzler E. Berg A (1987): Mortality in systemic lupus erythmatosus. J Rheumatol (suppl 13) 14:218-22.

Gladman DD, Goldsmith CH, Urowitz MB et al (1992): Cross-cultural validation and reliability of 3 disease activity indices in systemic lupus erythematosus. J Rheumatol 19: 608-11.

Gladman DD et al (1996): Systemic lupus international collaborating clinics conference on assessment of lupus flare and quality of life measures in SLE. J Rheumatol 23 (11): 1953-1955.

Gladman D, Ginzler E, Goldsmith C et al (1992): Systemic lupus international collaborative clinics: Development of a damage index in systemic lupus erythematosus (workshop report). J Rheumatol 19:1820-1.

Gladman D, Ginzler E, Goldsmith C et al (1996): The development and initial validation of the SLICC/ ACR damage index for SLE. Arthritis Rheum 39:363-9.

Gladman DD (1994): Indicators of disease activity, prognosis and treatment of systemic lupus erythematosus. Curr Opin Rheumatol 6:487.

Gladman DD et al. (1996): Lack of correlation among the 3 outcomes describing SLE: disease activity, damage and quality of life. Clinical & Experimental Rheumatology 14 (3): 305-8

Gladman DD. et al. (1996): A comparison of five health status instruments in patients with systemic lupus erythematosus. Lupus. 5(3); 190-5.

Guyatt GH, Feeny DH, Patrick DL (1993): Measuring health-related quality of life. Annals of Internal Medicine 118 (8): 622-629.

Guyatt GH, Bombardier C, Tugwell PX (1986): Measuring disease-specific quality of life in clinical trials. CMAJ 134: 889-895.

Hay EM, Bacon PA, Gordon C, et al (1993): The BILAG index: A reliable and valid instrument for measuring clinical disease activity in systemic lupus erythemetosus. Q J Med 86:447-58.

Hanly JG (1997): Disease activity, cumulative damage and quality of life in systemic lupus erythematosus: results of a cross-sectional study. Lupus 6(3): 243-7

Hochberg MC (1990): Systemic lupus erythematosus. Rheum Dis Clin Am 16: 617-639.

Hopkinson ND. Doherty M. Pawell R J (1994): Clinical features and race-specific incidence/ prevalence rates of systemic lupus erythematosus in a geographically complete cohort of patients. Ann Rheum Dis 53: 675-680.

Hochberg MC (1997): Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus (letter). Arthritis Rheum 40 (9): 1725.

Isenberg DA. Bacon PA, Bombardier C et al (1989): Criteria for assessing disease activity in systemic lupus erythematosus. J Rheumatol 16: 1395-6.

Jonsson H. Nived O, Sturfelt G (1989): Outcome in systemic lupus erythematosus: a prospective study of patients from a defined population. Medicine (Baltimore) 68:141-150.

Karlson EW et al (1997): The relationship of socioeconomic status, race, and modifiable risk factors to outcomes in patients with systemic lupus erythematosus. Arthritis Rheum 40 47-56.

Kind P (1995): The EuroQol Instrument: An Index of Health-Related Quality of Life. In: Spilker B, editor. Quality of Life and Pharmacoeconomics in Clinical Trials. Second Ed. Philadelphia: Lippincott-Raven Publishers 191-201.

Kosinski M (1997): Interpreting health status scores in clinical settings: Illustrating using the SF-36 health survey. Medical Outcome trust Bulletin. 1(1):20-21.

Kraemer HC, Thiemann S. How many subjects: statistical power analysis in research. London: Sage Publications, Inc, 1989.

Liang MH, Socher SA, Roberts WN, Esdaile JM (1988): Measurement of systemic lupus erythematosus activity in clinical research. Arthritis Rheum 31: 817-825.

Liang MH, Sten S, Esdaile JM (1988): Towards an operational definition of SLE activity for clinical research. Clin Rheum Dis 14:57-66.

Liang MH, Socher SA, Larson MG, Schur PH (1989): Reliability and validity of six systemic lupus erythemetosus. Arthritis Rheum 32 1107-18.

Liang MH (1987): The historical and conceptual framework for functional assessment in rheumatic disease. J Rheumatol 14 (Suppl. 14): 2-5.

McCarty DJ, Manzi S, Mdesger Jr TA et al (1995): Incidence of systemic lupus erythematosus: race and gender differences. Arthritis Rheum 38: 1260-70.

Michet C J et al (1985): Epidemiology of systemic lupus erythematosus and other connective tissue diseases in Rochester. Minnesota. 1950-1979. Mayo Clin Proc 60:105-113.

Mills JA (1994): Systemic lupus erythematosus. N Engl J Med 330: 1871-9.

Naughton MJ, Shumaker SA (1997): Assessment of health-related quality of life in orthopaedic outcomes' studies. J Arthroscopic and Related Surgery 13 (1): 107-113.

Nelson EC (1997): Quality improvement and the patient's perspective of care: Learning from satisfaction against need. Medical Outcomes Trust Bulletin 1 (1): 18-19.

Patrick DL, Erickson P(1993): Health Status and Health Policy. New York: Oxford University Press,

Petri M, Hellmann D, Hochberg M (1992): Validity and reliability of lupus activity measures in the routine clinic setting J Rheumatol 19: 53-9.

Pistiner M,Wallance DJ, Nessim S, Metzger AL, Klinenberg JR (1991): Lupus erythematosus in the 1980s: a survey of 570 patients. Semin Arthritis Rheum 22: 55-64.

Petri M, Hellmann D, Hochberg M (1989): Validity and reliability of lupus activity index (LAI): comparison with the Toronto Activity Index (SLEDAI) and Systemic Lupus Activity Measure (SLAM) (abstract). Arthritis Rheum 32 (suppl 4): S30. S 93.

Pincus T, Callahan LF, Vaughn WK (1987): Questionnaire, walking time and button test measures of functional capacity as predictive markers for mortality in rheumatoid arthritis. J Rheumatology 14: 240-251.

Reveille JD, Bartolucci A, Alarcon GS (1990): Prognosis in systemic lupus erythematosus: negative impact of increasing age at onset, Black race, and thrombocytopenia, as well as causes of death. Arthritis Rheum 33:37-48.

Ruta DA, Hurst NP, Kind P et al(1998): Measuring health status in British Patients with Rheumatoid Arthritis: Reliability, Validity and Responsiveness of The Short form 36-item Health Survey (SF-36) British Journal of Rheumatology 37: 425-436.

Stafford-Brady FJ, Urowitz MB, Gladman DD, et al (1988): Lupus retinopathy: patterns, associations, and prognosis. Arthritis Rheum 31: 1105-10.

Schroeder JO, Euler HH (1997): Recognition and Management of Systemic Lupus Erythematosus. Drugs 54: 422-434.

Stein H, Walters K et al (1986): Systemic Lupus Erythematosus: a medical and social profile. J Rheumatol 13: 570-576.

Stewart AL, Hays RD, Ware JE (1988): The MOS short-form general health survey: reliability and validity in a patient population. Med Care 26: 724-735.

Stock SR, Cole DC, Tugwell P, and Streiner D (1996): Review of applicability of existing functional status measures to the study of workers with musculoskeletal disorders of the neck and upper limb. American Journal of Industrial Medicine 29: 679-688.

Stoll T, Seifert B, Isenberg DA(1996): SLICC/ACR damage Index is a valid, and renal and pulmonary organ scores are predictor of severe outcome in patients with systemic lupus erythematosus. Br J Rheumatol 35 248-54.

Stoll T, Stucki G et al (1996): Further validity of the BILAG disease activity index in patients with systemic lupus erythematosus (SLE). Br J Rheumatoid 35: 39.

Stoll T. Gordon C. et al (1997): Consistency and validity of patients administered assessment of quality of life by the MOS SF-36; its association with disease activity and damage in patients with systemic lupus erythematosus. J Rheumatol 24 (8): 1608-14.

Symmons DPM, Coppock JS, Bacon PA et al (1988): Development and assessment of a computerized index of clinical disease activity in systemic lupus erythematosus. Quart J Med 69: 927-37.

Swaak AJ, Nossent JC, Bronsveld W et al (1989): Systemic lupus erythematosus. I: Outcome and survival. Dutch experience with 110 patients studied prospectively. Ann Rheum Dis 48: 447-54.

Tan Em, Cohen AS, Fries TF.et, al (1982): The 1982 revised criteria for the classification of systemic lupus erythemotosus. Arthritis Rheum 25: 1271-718.

Testa MA, Simonson DC (1996): Assessment of quality- of- life outcomes. The New England Journal of Medicine 334: 835-840.

The EuroQol group (1990): EuroQol A new facility for the measurement of health related quality of life. Health Policy 16: 199-208.

Urowitz MB, Gladman DD, Tozman ECS, Goldsmith CH (1984): The lupus activity criteria count. J Rheumatol 11: 783-787.

Vitali C, Bencivelli W, Isenberg DA et al (1992): Disease activity in systemic lupus erythematosus: Report of the consensus study group of the European workshop for Rheumatology. Research II. Identification of the variables indicative of disease activity and their use in the development of an activity score. The European consensus study group for disease activity in SLE. Clin Exp Rheumatol 10: 541-7.

Ware, J.E., Sherbourne, C.D (1992): The MOS 36-Item Short-Form Health Survey (SF-36) I Conceptual framework and item selection. Med Care 30: 473-483.

Ware, JE., Kosiniski, M.,& Keller,S.D (1994). SF-36 Physical and Mental Health scales: A user's manual. Boston: The health Institute, New England Medical Center.

Ward MM, Pyun E, Studenski S (1995): Long-term survival in systemic lupus erythematosus: patient characteristics associated with poorer outcomes. Arthritis Rheum 38: 274-83.

Wilson IB, Cleary PD(1995); Linking clinical variables with health-related quality of life: A conceptual model of patient outcomes. JAMA 1:59-65.

World health Organization (1980): International classification of impairments, disabilities, and handicaps: a manual of classification relating to the consequences of disease. Geneva: World Health Organization.

Wolfe F, Kleinheksal SM, Cathey MA, Hanly DHJ, Spitz P (1991): Antecedents of mortality in rheumatoid arthritis: a study of 1405 patients with RA in a community setting (abstract). Arthritis & Rheumatism 34 (Suppl 9): S48.

Wood-Dauphinee S (1999). Assessing quality of life in clinical research: from where have we come and where are we going? J Clin Epidemiol (in press).

APPENDIX A

INSTRUMENTATION

A1) Clinical Data Form

A2) SLE Activity Measure-2

A3) SLEDAI Form

A4) SLICC/ACR Form

A5) EuroQol Questionnaire

A6) SF-36 Health Status Survey

Clinical Data Form

Subject no. _____ **Key no.**_____

Date:_____

A) Demographic Data

First name _____last name _____ Maiden name_____

Age (years):_____ **Sex:** ___male ____female

Address: _____
Number Street name Apt#

_____
City Province Postal code phone number_____

Ethnic Origin _____ Caucasian
_____Black
_____ Asian
_____ Native American
_____Other(specify)_____

Marital Status: Single Married Divorced/Separated Widowed

Occupation: Yes___ No___

B) Education What is the highest year of schooling you have completed

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17

Elementary High School Cegep University

C) 1c: Employment

2c: Disability (permanent and temporary disability)

D) Previous Medical and Surgical history

Yes _____ Specify_____
No _____

E) Clinical Data

Diagnosis Year:_____

>=4 ARA SLE criteria Yes_____ No_____

Disease duration (years)_____

Medication usage _____

Prednisone___

NSAID____

Gold____

Other disease modifying_____

No drugs_____

SLE ACTIVITY MEASURE-2

(Present Last Month)

NAME_____

IDENTIFICATION								
0	0	0	0	0	0	0	0	0
1	1	1	1	1	1	1	1	1
2	2	2	2	2	2	2	2	2
3	3	3	3	3	3	3	3	3
4	4	4	4	4	4	4	4	4
5	5	5	5	5	5	5	5	5
6	6	6	6	6	6	6	6	6
7	7	7	7	7	7	7	7	7
8	8	8	8	8	8	8	8	8
9	9	9	9	9	9	9	9	9

VISIT DATE		
MONTH	DAY	YEAR
○ Jan		
○ Feb		
○ Mar	0 0	0 0
○ April	1 1	1 1
○ May	2 2	2 2
○ June	3 3	3 3
○ July	4 4	4
○ Aug	5 5	5
○ Sept	6 6	6
○ Oct	7 7	7
○ Nov	8 8	8
○ Dec	9 9	9

CONSTITUTIONAL

1. **Weight loss**
   - ⓪ Absent
   - ① ≤10% body weight
   - ③ >10% body weight
   - ○ Unknown
2. **Fatigue**
   - ⓪ Absent
   - ① Little or no limit on normal activity
   - ② Limits normal activity
   - ○ Unknown
3. **Fever**
   - ⓪ Absent
   - ① 37.5-38.5°C or 99.5-101.3°F
   - ③ >38.5°C or >101.3°F
   - ○ Unknown

INTEGUMENT

4. **Oral/nasal ulcers, periungal erythema, malar rash, photosensitive rash, *or* nail fold infarct**
   - ⓪ Absent
   - ① Present
   - ○ Unknown
5. **Alopecia**
   - ⓪ Absent
   - ① Hair loss with trauma
   - ② Alopecia observed
   - ○ Unknown
6. **Erythematous, macular or papular rash, discoid lupus, lupus profundus, *or* bullous lesions**
   - ⓪ Absent
   - ① <20% Total Body Surface Area (TBA)
   - ② 20-50% TBA
   - ③ >50% TBA
   - ○ Unknown
7. **Vasculitis (leucocytoclastic vasculitis, urticaria, palpable purpura, livédo reticularis, ulcer *or* panniculitis)**
   - ⓪ Absent
   - ① <20% TBA
   - ② 20-50% TBA
   - ③ >50% TBA or necrosis
   - ○ Unknown

EYE

8. **Cytoid bodies**
   - ⓪ Absent
   - ① Present
   - ③ Visual acuity <20/200
   - ○ Unknown
9. **Hemorrhages (retinal or choroidal) or episcleritis**
   - ⓪ Absent
   - ① Present
   - ③ Visual acuity <20/200
   - ○ Unknown
10. **Papillitis or pseudotumor cerebri**
    - ⓪ Absent
    - ① Present
    - ③ Visual acuity <20/200 or field cut
    - ○ Unknown

RETICULOENDOTHELIAL

11. **Lymphadenopathy**
    - ⓪ Absent
    - ① Shotty
    - ② Diffuse or nodes >1cm x 1.5cm
    - ○ Unknown
12. **Hepato- or splenomegaly**
    - ⓪ Absent
    - ① Palpable only with inspiration
    - ② Palpable without inspiration
    - ○ Unknown

PULMONARY

13. **Pleurisy/pleural effusion**
    - ⓪ Absent
    - ① Shortness of breath or pleuritic pain
    - ② Shortness of breath or pleuritic pain **with exercise**
    - ③ Shortness of breath or pleuritic pain **at rest**
    - ○ Unknown

CARDIOVASCULAR

14. **Raynaud's**
    - ⓪ Absent
    - ① Present
    - ○ Unknown
15. **Hypertension (diastolic pressure, mm Hg)**
    - ⓪ <90
    - ① 90-104
    - ② 105-114
    - ③ ≥115
    - ○ Unknown
16. **Pericarditis/carditis**
    - ⓪ Absent
    - ② Postitional chest pain or arrhythmia
    - ③ Myocarditis with hemodynamic compromise &/or arrhythmia
    - ○ Unknown

GASTROINTESTINAL

17. Abdominal pain (serositis, pancreatitis, *or* ischemic bowel, etc.)
- ⓪ Absent
- ① Complaint
- ② Limiting pain
- ③ Peritoneal signs/ascites
- ○ Unknown

NEUROMOTOR

18. Stroke syndrome (includes mononeuritis multiplex, reversible neurologic deficit (RND), cerebrovascular accident (CVA), *or* retinal vascular thrombosis)
- ⓪ Absent
- ② RND, mononeuritis multiplex, cranial neuropathy *or* chorea
- ③ CVA, myelopathy, *or* retinal vascular occlusion
- ○ Unknown

19. Seizure
- ⓪ Absent
- ② 1 or more/month
- ③ Status epilepticus
- ○ Unknown

20. Cortical dysfunction
- ⓪ Absent
- ① Mild depression/personality disorder or cognitive deficit
- ② Change in sensorium, severe depression, *or* limiting cognitive impairment
- ③ Psychosis, dementia, *or* coma
- ○ Unknown

21. Headache (including migraine equivalents and aseptic meningitis)
- ⓪ Absent
- ① Symptoms only
- ② Interferes with normal activities/aseptic meningitis
- ○ Unknown

22. Myalgia/myositis
- ⓪ Absent
- ① Symptoms only
- ② Limits some activity
- ③ Incapacitating
- ○ Unknown

JOINTS

23. Joint pain
- ⓪ Absent
- ① Arthralgia only
- ② Objective synovitis
- ③ Limits function
- ○ Not recorded

LABORATORY

25. Hematocrit (ml/dL)
- ⓪ >35
- ① 30-35
- ② 25-29
- ③ <25
- ○ Not recorded

26. White blood cell count (per mm³)
- ⓪ >3500
- ① 2000-3500
- ② 1000-1999
- ③ <1000
- ○ Not recorded

27. Lymphocyte count (per mm³)
- ⓪ 1500-4000
- ① 1000-1499
- ② 500-999
- ③ <500
- ○ Not recorded

28. Platelet count (x1000 per mm³)
- ⓪ >150
- ① 100-150
- ② 50-99
- ③ < 50
- ○ Not recorded

29. Westergren ESR (mm/hr)
- ⓪ <25
- ① 25-50
- ② 51-75
- ③ >75
- ○ Not recorded

30. Serum creatinine (mg/dL) or creatinine clearance (% normal)
- ⓪ 0.5-1.3 or 80-100%
- ① 1.4-2 or 60-79%
- ② 2.1-4 or 30-59%
- ③ >4 or < 30%
- ○ Not recorded

31. Urine sediment (per hpf)
- ⓪ Normal
- ① 6-10 RBC or 6-10 WBC; *or* 0-3 granular or 0-3 non RBC casts; *or* trace to 1+ (<500 mg/l 24° urine protein)
- ② 11-25 RBC or 11-25 WBC; *or* >3 granular or >3 non RBC casts; *or* 2 to 3+ (≥500 mg-3.5 g/l 24° urine protein)
- ③ >25 RBC or >25 WBC; *or* any RBC cast; *or* 4+ (>3.5 g/l 24° urine protein)
- ○ Not recorded

Total score (sum of bubbles) _____

SLEDAI Form
LUPUS REGISTRY
Pathkey: _____
Today's Date: ___/____/___

(Enter weight in SLEDAI score column if descriptor present at the time of the visit or in the preceding 10 days)

Weight	SLEDAI score	Descriptor	Definition
8	____	Seizure	Recent onset. Exclude metabolic, infectious or drug causes.
8	____	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, improvised thought content, marked illogical thinking, bizarre, disorganized or catatonic behaviour. Exclude presence of uraemia and offending drugs.
8	____	Organic Brain Syndrome	Altered mental function with impaired orientation, memory or other intellectual function with rapid onset, fluctuating clinical features. Such as any of the following: a) clouding of consciousness with reduced capacity to focus and inability to sustain attention to environment. Plus at least 2 of b) of perceptual disturbance; incoherent speech; insomnia or daytime drowsiness; increased or decreased psychomotor activity. (Exclude metabolic, infectious, drug causes).
8	____	Visual	Retinal changes of SLE; any of cytoid bodies, retinal haemorrhages, serous exudate or haemorrhages in the choroid, optic neuritis. (Not due to hypertension or drugs or infection).
8	____	Cranial Nerve	New onset of sensory or motor neuropathy involving cranial nerves.
8	____	Lupus Headaches	Severe, persistent headache, may be migraines, but must be non-responsive to narcotic analgesia.
8	____	CVA	New syndrome. Exclude arteriosclerosis.
8	____	Vasculitis	Ulcerations, gangrene, tender finger nodules, periungual infarction, splinter haemorrhages, biopsy or angiogram proof of vasculitis.
4	____	Arthritis	More than 2 joints with pain and signs of inflammation (ie. Tenderness, swelling, or effusion).
4	____	Myositis	Proximal muscle aching/weakness, associated with elevated CPK/aldolase or EMG changes or a biopsy showing myositis.
4	____	Casts	Heme granular or RBC.
4	____	Haematuria	> 5 RBC/HPF. Excluding other causes (stone, infection).
4	____	Proteinuria	> 0.5 g/24 hours. New onset or recent increase of more than 0.5 g/24 hrs.
4	____	Pyuria	> 5 WBC/HPF. Exclude infection.
2	____	New Rash	New onset or recurrence of inflammatory type rash.
2	____	Alopecia	New or recurrent. An abnormal patch of diffuse loss of hair.
2	____	Mucous membrane	New onset or recurrence of oral or nasal ulcerations.
2	____	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	____	Pericarditis	Pericardial pain with at least one of the following: rub, effusion, ECG, echo confirmation.
2	____	Low Complement	Decreased any of CH50, C3, C4. Below the lower limit of normal for lab.
2	____	Increased DNA binding	> 25% binding by Farr assay. Above normal range of lab value (eg.25%).
1	____	Fever	> 38°C. After exclusion of infection.
1	____	Thrombocytopenia	< 100,000 platelets.
1	____	Leucopenia	WBC < 3000 (not due to drugs).

SLICC-R/ACR Form
LUPUS REGISTRY
Pathkey:__ __ __
Date:__/____/__

SYSTEMIC LUPUS INTERNATIONAL COLLABORATING CLINICS (SLICC)		
Damage occurring since diagnosis of lupus, ascertained by clinical assessment and present for at least 6 months unless otherwise stated. Repeat episodes mean at least 6 months apart to score 2. The same lesion cannot be scored twice.		
ITEM	SCORE (circle)	
OCULAR (Either eye, by clinical assessment)		
Any cataract ever	0 1	
Retinal change OR optic atrophy	0 1	
NEUROPSYCHIATRIC		
Cognitive impairment (e.g. memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance level)	0 1	
OR Major psychosis		
Seizures requiring therapy for 6 months	0 1	
Cerebral vascular accident ever (Score 2 if >1), resection not for malignancy	0 1	2
Cranial or peripheral neuropathy (excluding optic)		
Transverse myelitis	0 1	
	0 1	
RENAL		
Estimated or measured GFR < 50%	0 1	
Proteinuria 24h, ≥ 3.5 g	0 1	
OR		
End-stage renal disease (regardless of dialysis or transplantation)	3	
PULMONARY		
Pulmonary hypertension (right ventricular prominence, or loud P2)	0 1	
Pulmonary fibrosis (physical and X-ray)	0 1	
Shrinking lung (X-ray)	0 1	
Pleural fibrosis (X-ray)	0 1	
Pulmonary infarction (X-ray) OR resection not for malignancy	0 1	
CARDIOVASCULAR		
Angina OR coronary artery bypass	0 1	
Myocardial infarction ever (Score 2 if > 1)	0 1	2
Cardiomyopathy (ventricular dysfunction)	0 1	
Valvular disease (diastolic murmur, or a systolic murmur > 3/6)	0 1	
Pericarditis x 6 months or pericardiectomy	0 1	

Pathkey:__ __ - __ __ __

SLE DAMAGE INDEX - Page 2			
PERIPHERAL VASCULAR			
Claudication x 6 months	0	1	
Minor tissue loss (pulp space)	0	1	
Significant tissue loss ever (eg. loss of digit or limb, resection) (Score 2 if >1)	0	1	2
Venous thrombosis with swelling, ulceration, OR venous stasis	0	1	
GASTROINTESTINAL			
Infarction or resection of bowel (below duodenum), spleen, liver or gall bladder ever (Score 2 if >1)	0	1	2
Mesenteric insufficiency	0	1	
Chronic peritonitis	0	1	
Stricture OR upper gastrointestinal tract surgery ever	0	1	
Pancreatic insufficiency requiring enzyme replacement or with pseudocyst	0	1	
MUSCULOSKELETAL			
Atrophy or weakness	0	1	
Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis)	0	1	
Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)	0	1	
Avascular necrosis (Score 2 if > 1)	0	1	2
Osteomyelitis	0	1	
Ruptured tendons	0	1	
SKIN			
Alopecia	0	1	
Extensive scarring or panniculum other than scalp and pulp space	0	1	
PREMATURE GONADAL FAILURE	0	1	
DIABETES (regardless of treatment)	0	1	
MALIGNANCY (exclude dysplasia)	0	1	2

Your own health state today

By placing a tick in one box in each group below, please indicate which statement best describes your own health state today.

Do not tick more than one box in each group.

Mobility

I have no problems in walking about	☐
I have some problems in walking about	☐
I am confined to bed	☐

Self-Care

I have no problems with self-care	☐
I have some problems washing or dressing myself	☐
I am unable to wash or dress myself	☐

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	☐
I have some problems with performing my usual activities	☐
I am unable to perform my usual activities	☐

Pain/Discomfort

I have no pain or discomfort	☐
I have moderate pain or discomfort	☐
I have extreme pain or discomfort	☐

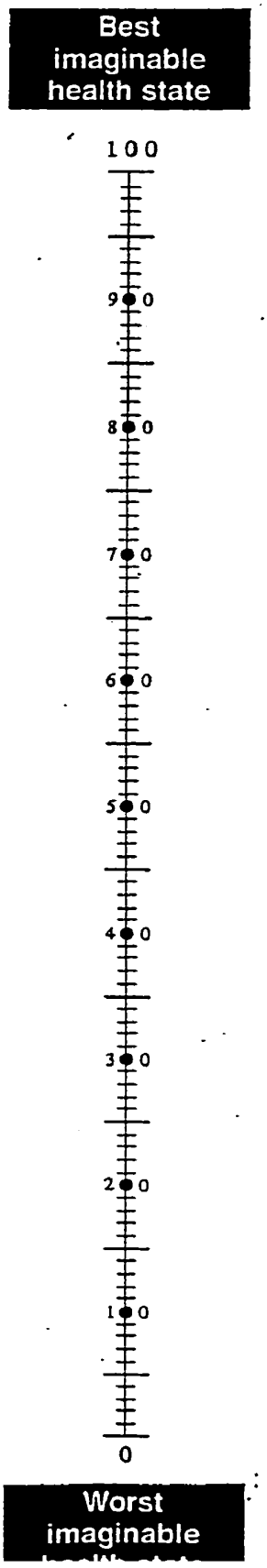
Anxiety/Depression

I am not anxious or depressed	☐
I am moderately anxious or depressed	☐
I am extremely anxious or depressed	☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked by 100 and the worst state you can imagine is marked by 0.

We would like you to indicate on this scale how good or bad is your own health today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your current health state is.

Your own health state today



SF - 36 Form
LUPUS REGISTRY
Pathkey:___ ___ ___
Date: _____

INSTRUCTIONS: This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is:

(Circle one)

Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

2. Compared to one year ago, how would you rate your health in general now?

(Circle one)

Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same as one year ago	3
Somewhat worse now than one year ago	4
Much worse now than one year ago	5

Copyright ©1992 Medical Outcomes Trust
All rights reserved.
(SF-36 Standard U.S. Version 1.0)

Pathkey:_____ _____ _____

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(Circle one number on each line)

ACTIVITIES	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
a. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing **several** flights of stairs	1	2	3
e. Climbing **one** flight of stairs	1	2	3
f. Bending, kneeling, or stooping	1	2	3
g. Walking **more than a mile**	1	2	3
h. Walking **several blocks**	1	2	3
i. Walking **one block**	1	2	3
j. Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health ?

(Circle one number on each line)

	YES	NO
a. Cut down on the **amount of time** you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Were limited in the **kind** of work or other activities	1	2
d. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

Copyright ©1992 Medical Outcomes Trust
All rights reserved.
(SF-36Standard U.S. Version 1.0)

Pathkey:_____ _____ _____

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(Circle one number on each line)

	YES	NO
a. Cut down on the **amount of time** you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Didn't do work or other activities as **carefully** as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

(Circle one)

Not at all 1
Slightly 2
Moderately 3
Quite a bit 4
Extremely 5

7. How much bodily pain have you had during the past 4 weeks?

(Circle one)

None 1
Very mild 2
Mild 3
Moderate 4
Severe 5
Very severe 6

Copyright ©1992 Medical Outcomes Trust
All rights reserved.
(SF-36Standard U.S. Version 1.0)

Pathkey:_____ _____ _____

8. During the past 4 weeks, how much did pain, interfere with your normal work (including both work outside the home and housework)?

(Circle one)

Not at all	1
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks?

	All of the Time	Most of the Time	A Good Bit of the time	Some of the Time	A Little of the Time	None of the Time
a. Did you feel full of pep?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6
f. Have you felt downhearted and blue?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

Copyright ©1992 Medical Outcomes Trust
All rights reserved.
(SF-36Standard U.S. Version 1.0)

Pathkey:

10. During the past 4 weeks, how much of the time has your physical or emotional problems interfered with your social activities (like visiting with friends, relatives, etc)?

(Circle one)

All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

11. How TRUE or FALSE is each of the following statements for you?

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get sick a little easier than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent_____	1	2	3	4	5 p2

Copyright ©1992 Medical Outcomes Trust
All rights reserved.
(SF-36Standard U.S. Version 1.0)

APPENDIX B

Fig B.1 Impact on Self-rate Health of a Problem in One of the Dimensions of the EQ-5D

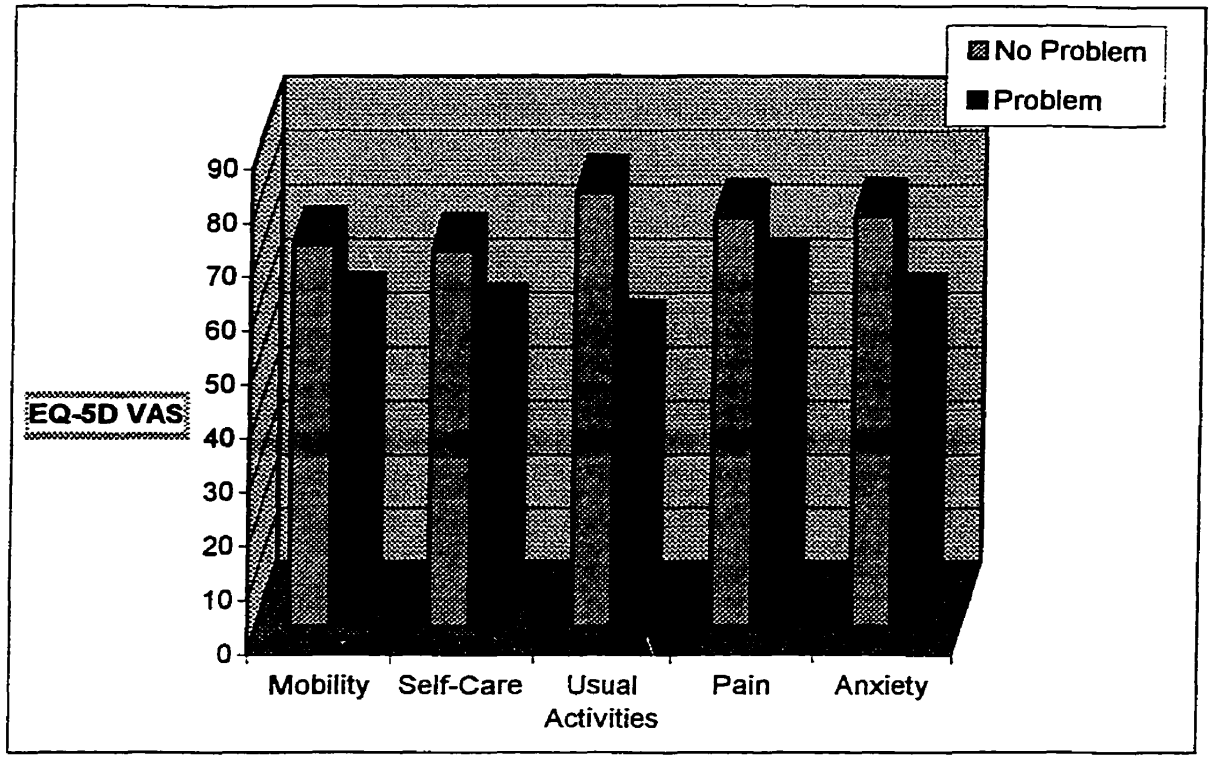


Fig B.2 : Impact on PCS (SF-36) of a Problem in One of the Dimensions of the EQ-5D

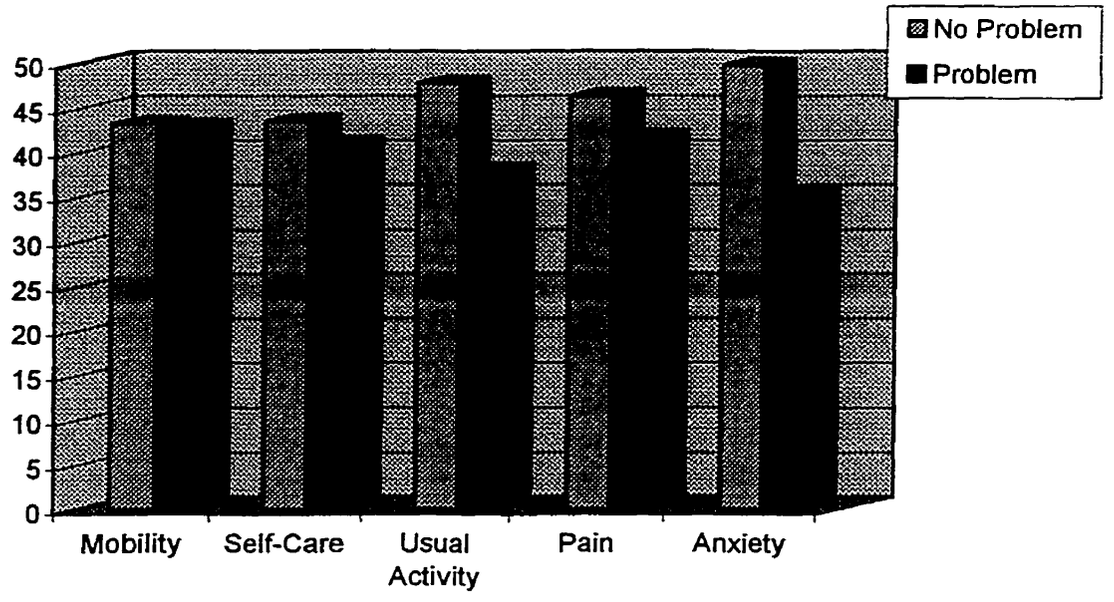
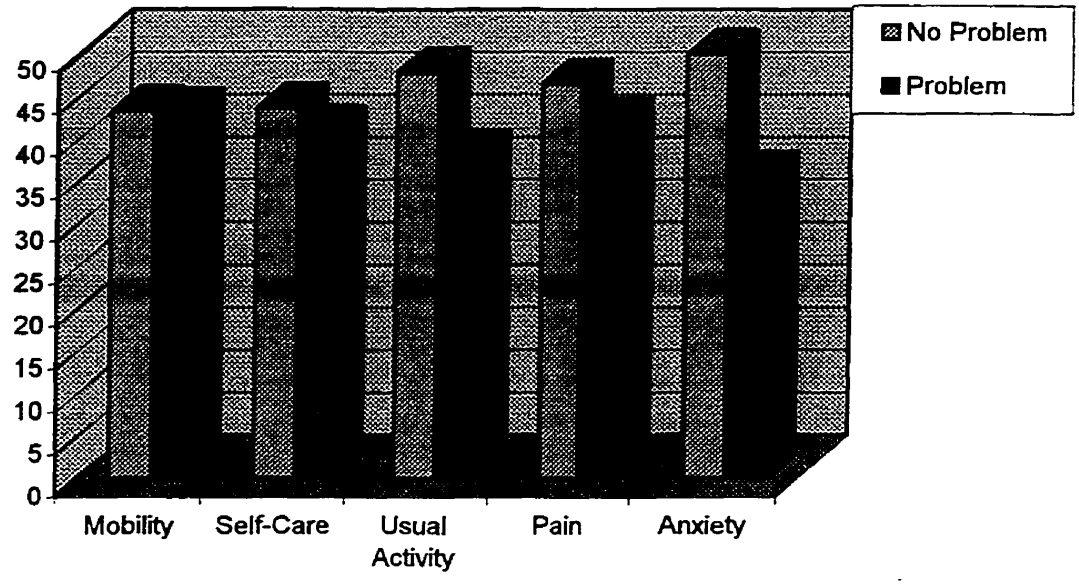


Fig B. 3 : Impact of MCS (SF-36) on a Problem in One of the Dimensions of the EQ-5D



APPENDIX C

The Ethics Committee of the Montreal General Hospital from which patients were recruited approved an English and French version of the consent form for this study. English and French consent forms, and the research ethics application form for approval of the clinical research proposal are presented with a letter dated January 21,1998 granting approval for this study

PATIENT CONSENT FORM
Rheumatology and Immunology Department
MONTREAL GENERAL HOSPITAL
McGill University

Title of the Study: Evaluating Disease Activity in Systemic Lupus Erythematosus: The Role of Clinical and Health Status Measures

Introduction: Researchers at the Montreal General Hospital and McGill University are conducting a study about the health of persons with Systemic Lupus Erythematosus (SLE). This study will evaluate the relationship between clinical and laboratory measures of lupus disease activity and health status.

Procedures: We are asking if you would like to participate in this study. If you agree we will assess your health with two questionnaires. Each questionnaire usually takes about 5 to 10 minutes to complete, depending on the individual.

If you agree to participate, the doctor examining you will fill out two forms about your disease and this data will be shared with the researchers, as will the results of any laboratory tests ordered by your doctor. If you don't wish to participate, this information will still be collected but it will not be shared with the research team. The information about whether you are participating or not will not be communicated to the doctor examing you at this visit.

Participation and Confidentiality: Participation is voluntary. You may refuse to participate or withdraw from the study at any time without this having an effect on the care you receive while in the hospital or after. All of the information that we obtain from you will be kept strictly confidential. The data will be kept in a locked filing cabinet in the investigator's office. You will be assigned a study number and this will be the only identifying mark that will appear on your results. The results of the study will be published in scientific journals but your data will appear as numbers in statistical summaries.

Risks: We do not anticipate any risks or inconvenience to you if you participate in the study. You should not experience any discomfort during or after the study procedure since we will only ask you to answer questionnaires.

Benefits: The results of this study will help us better understand how SLE affects the physical function and global health of an individual. It will also contribute to the overall

knowledge on the methods to evaluate the treatment of SLE and to our understanding of biological and clinical processes that contribute to health related quality of life in SLE.

Contact Numbers: If you have any questions about the research, please contact the investigator, Dr.Chenchen Wang at (514)-842-1231 ext. 6906 at the Royal Victoria Hospital. Dr. Paul Fortin at (514)-937-6011 ext 4718 at the Montreal General Hospital. Dr. Nancy Mayo at (514)-842-1231 ext. 6925.

By signing this consent form you acknowledge that the study has been explained to you and that you understand the contents of this consent form. You agree that you have had the opportunity to ask questions, that your questions have been answered to your satisfaction and you agree to participate in the study.

Declaration of the Participant: I understand what is involved in the study that I have been invited to join and I agree to participate in this study " Evaluation of health status in SLE ".
A copy of this consent form has been given to the participant named below.

Signatures **Print Name** **Date**

Participant

Witness

DECLARATION DU PARTICIPANT:

En signant cette formule de consentement, je reconnaît que l'étude m'a été expliquée, et que je comprends le contenu de cette formule de consentement. Je reconnaît que j'ai eu l'occasion de demander des questions, que des réponses à ces questions m'ont été fournies de façon satisfaisante, et que j'accepte de participer à l'étude.

Je comprends ce qui est impliqué dans cette étude, à laquelle on m'a demandé de participer, et je suis d'accord pour participer à cette étude sur " L'évaluation de l'Etat de Santé dans le LED". Une copie de cette formule de consentement me sera donnée.

Signatures	Nom en caractères moulés	Date
Investigateur/Délégué		
Participant		
Témoin		

F:\EQ5DCF.FR

MONTREAL GENERAL HOSPITAL AND
MONTREAL GENERAL HOSPITAL
RESEARCH INSTITUTE

RESEARCH ETHICS COMMITTEE AND
CLINICAL TRIALS COMMITTEE
APPLICATION FORM FOR APPROVAL
OF A CLINICAL RESEARCH PROPOSAL

I. **Title of research proposal:** Evaluating disease activity in Systemic Lupus Erythematosus: The role of biological, clinical and health status measures.

a). **Principal investigators and institutional affiliation:**

Dr. Chenchen Wang, Dr. Paul Fortin, Dr. Nancy Mayo.

Montreal General hospital Division of Rheumatology and Immunology Suite A6-140 1650 Cedar Montreal, QC H3G-1A4 Tel: 514-937-6011 ext.4718

b) **Co-investigator(s) and institutional affiliation:** Health Service and Outcome Group Royal Victoria Hospital Research Institute 687 Pie A.W., Montreal QC. H3A 1A1 McGill University. 842-1231ext. 6906

II. **Departments involved:** Rheumatology, Immunology, Epidemiology.

IV. **Granting agency or company:** N/A

V. **Period of grant (awarded or pending):**

VI. **Institutions involved:** Montreal General hospital, Royal Victoria hospital.

VII. **General information:** (Please answers the following questions if applicable)

a) Is this a Phase I, II, or III trial? N/A

b) In this study:

(I) Is there a control group? N/A

(ii) Is the trial randomized? N/A

(iii) Is there a placebo? N/A

(iv) Have requirements under the Canadian Health Protection Branch of FDA (US Food and Drug Application) been met, if applicable? N/A

(v) Has statistical justification for the study Design and sample size was provided? Y

c) If A no is answered to any of the above, please explain: The project is related the health status in SLE patients. Is this a National/International study? Yes____ No_X____ If yes, state whether: Epidemiology Y Clinical Research Y Both Y__ (Explain)

d)

e) To carry out a clinical research using epidemiology methods.

Location(s) or site(s) at which proposal project will be undertaken: Division of Rheumatology , Immunology, and Epidemiology in MGH. Division of Epidemiology in RVH.

VIII. **Conflict of interest or conflicting interests:**

It is important that the Research Ethics Committee and Clinical Trials Committee be aware of the nature of any arrangements that may **create a conflict of interest, or the appearance thereof,** between the investigator research responsibilities and a) the arrangement with the sponsor of the study, b) the investigator professional association with the participants in the study. There should be no conflicts, which could be perceived to adversely affect subjects enrolled in research projects. If there is any doubt as to the possibility of there being a conflict of interest, the onus is on the investigator to discuss the situation with the Research Ethics Committee Chair and to be aware of existing Hospital (or McGill University) conflicts of interest policy.

a) **Sponsors of the study.**

Are any of the investigators in this study receiving any direct personal remunerations or other personal or family financial benefits (either direct or indirect) for taking part in this investigation (Aother financial benefits may include contractual or consulting agreements, stock or shareholdings or future options with the sponsoring company, computing equipment, travel benefits, etc)?

Yes ____ No_X__ If yes, please append to this page a letter describing these activities in general. Detailed information may be submitted to the Dean or Hospital CEO in confidence.

b) Is there any reimbursement to the investigator for referring patients to a study?
Yes____ No_X_ Explain_____

c) **Study participants**

Are any of the investigators involved in this study employers, supervisors, or teachers of any of the individuals intended for study? Yes_____ No _X__ If yes,

please explain: _____

_____

d) **Other conflict of interest**
Do you see any other potential conflict of interest yes or no X . If so give details_____

_____

N.B. All agreements with drug companies or other industrial partners should ensure that a paragraph on publication rights is included. The following can be used as a guide:
A(company) requires that the investigator shall provide a copy of any manuscript or abstract involving oral presentation at least on e month prior to submission of that manuscript by the investigator for publication or presentation. Nothing in the foregoing shall be deemed to imply any editorial restriction of the contents of the manuscript and (company) accepts no responsibility for any consequences of publication of the manuscript by the investigators.

IX. **Please attach comments, if space is insufficient, addressing the following aspects of your research projects if they are not addressed clearly in your research protocol.**

a. **Purpose of the study:** The purpose of the study is to evaluate the relationship between clinical and biological markers of SLE disease activity and generic health status._____

b. **Description of the study (Methodology):** All patients seen for a regular SLE clinic visit at the Montreal General Hospital will be approached to participate in the cross-sectional study with an invitation letter that will be given to them at the time of registration. After obtaining informed consent, participants will fill out two questionnaires on health status (SF-36 and EQ-5D). The doctor examining each patient will have a SLE data form to complete which contains the relevant data fields. All of the data to be collected is part of the routine assessment. All data will be added to the existing patient database including the results of laboratory tests and chart data review. Approximate 20 to 30 patients are seen at each weekly clinic, so we expect to recruit approximate 50 patients over three months. The relationship between health status and clinical and biological markers will be analyzed using correlation and multivariable linear regression._____

_____

_____

c. **Selection of participants:** How will potential study participants be identified and recruited?_____
_____ All adult patients (>18 years old) with SLE as defined by the presence of four or more

of the 1997 revised diagnostic criteria of the American College of Rheumatology attending the Lupus Clinic at the Montreal General Hospital who agree to participate will be selected. Excluded will be patients who have additional chronic conditions independent of SLE that interfere with the assessment of outcome or alter the course of the disease.

d. **Inclusion and exclusion criteria:** Will minors or adults unable to consent be recruited? If yes, give details of the recruitment process.

No.

e. **Potential risks and discomfort:** All reasonable foreseeable risks, no matter how rare or minimal, must be disclosed as a risk in the consent form. This includes the risk(s) of not receiving treatment in a placebo-controlled study. (Indicate the expected frequency of these risks)

No, we will only ask the participants to fill out two questionnaires on health status so they should not experience any discomfort.

f. **Potential benefits:** (Should be explained but not overstated) The relationship between clinical, biological markers and Health Related Quality Of Life (HRQoL) will be examined in light of socio-demographic variables, drug therapy received, and duration of the disease. Previously validated lupus activity indices such as the Systemic Lupus Activity Index and the Systemic Lupus Erythematosus; Disease Activity Index will be used. This study will make an important contribution to knowledge of methods on the evaluation on of therapeutic interventions in SLE, and will contribute to our understanding of biological and clinical processes that contribute to HRQoL. Information on the relationship between measures of disease activity and health-related quality of life will assist patients and clinicians in understanding each other's point of view about the disease process. This may improve communication and compliance with treatment recommendations. Ultimately the results of this work will contribute to enhancing the understanding of SLE patient and the results of this study will have immediate applicability to the majority of persons with SLE.

g. **Risk-benefit ratio:**

N/A

h. **Consent procedures:** Who will obtain **informed consent** and how. Someone who normally has access to the confidential information of the potential participants medical file/record (in general, a member of the treating team) must first contact the potential participant to seek his/her assent (permission) to consider participation in the study. In addition, it is recommended that consent be subsequently obtained by a member of the research team who is not part of the treating team for that subject (to avoid a form of subtle coercion). The participation of minors or incompetent adults requires their assent if they understand the nature and consequences, as well as the consent of the person having parental authority, or of the mandatory, tutor, or curator, except in cases of surveys where the next of kin may provide surrogate consent.

Dr. Chenchen Wang will give an information package to each patient upon registration at the clinic. This package will contain a letter introducing the research project, a consent form to sign and the questionnaires to be filled out. Dr. Chenchen Wang will be site to answer to any questions. After obtaining informed consent, participants will fill out two questionnaires on health status (SF-36 and EQ-5D).

i. **Alternative or standard therapy:** Describe alternative procedures or treatments. How does the study procedure treatment compare with standard care in the current state of knowledge?

N/A

j. **Occupational risk (to researchers or assistants):** Describe, if applicable, any risk to the personnel involved in the study. Will their be vaccination and/or monitoring for viral infections in studies involving manipulation of body fluids?

N/A

k. **Protection of confidentiality:** How will the confidentiality of research data be protected?

All information from this study will be kept strictly confidential. The name of patients will never be used in any report of this study. Confidentiality pertaining to this study will be kept by using a coded identification number on all data collection sheets with a key code list kept in locked filing cabinet in the investigators office. The research records will be handled as confidentially as possible within the law. Also, all the research records at the Montreal General Hospital and the Montreal General hospital Research Institute can be reviewed by the Research Ethics Committees

to make sure that institutional regulations regarding research involving humans are followed.

I. **Impact on nursing resources:** If nursing resources are required, please provide documentation (e.g. letter from head-nurse or nursing supervisor) that the resources available are sufficient to conduct the study.

N/A

X. **Advertisement:** Will any form of advertisement be used to recruit participants:
Yes____ No_X_. If yes, explain and provide a copy of any written advertisement:

XI. **Indemnification:** Will any form of compensation be given to the subjects:
Yes____ No_X_. If yes, provide a the details and a copy of any written policy:

XII. **For projects conducted with support of an industrial or commercial sponsor, the investigator(s) should make certain that an indemnification clause is included in their**

XIII. **contract with the sponsor to protect them and the Montreal General Hospital and Montreal General Hospital Research Institute from potential liability arising from the project.**

XIII. **Signatures**

Principal Investigator	**(Print name)**
Co-Investigator(s)	**(Print name)**
Co-Investigator(s)	**(Print name)**

Date

Appendix D

Additional Methodological Information

D.1 Eligibility Criteria

D.2 Sample Size Calculation

Eligibility Criteria

Inclusion Criteria:

1. Adults (> 18 years old) with SLE.
2. As defined by the presence of four or more of the revised diagnostic criteria of the American College of Rheumatology (formally the American Rheumatology Association ARA).
3. Patients attending the Lupus Clinic at the Montreal General Hospital and asking for their consent and those who agree to participate.

Exclusion Criteria:

Excluded patients who have additional chronic conditions, independent of SLE, that interfere with the assessment of outcome or alter the course of the disease.

Sample Size Calculation

The total sample size estimated in our study is 50 individuals. For a correlation of 0.5 between two measures, for 90% power, and a two-tailed alpha level of significance of 0.05, 38 subjects are required. The formula $n = v + p + 1$ (Kraemer and Thiemann) was used to adjust for multiple variables, where:

n = the total number of subjects

v = the sample size for sample correlation

p = the number of additional variables included in the model

Therefore,

$n = 38 + 11 + 1$

N= 50.

Appendix E

Table E: Peason Correlaiton Coefficient for Outcome Measures (n=54)

APPENDIX D

Table D.1: Peason Correlation Coefficient for Outcome Measures (n=54)

	Age	Duration	SLAM-2	SLEDAI	SLICC	MD-VAS	P-VAS	EQ-5D-VAS	PCS
Age									
Duration	**0.56******								
SLAM-2	**-0.27***	**-0.27***							
SLEDAI	**-0.32***	-0.19	**0.45 *****						
SLICC	-0.01	0.19	**0.37****	0.22					
MD-VAS	-0.11	-0.13	**0.60******	**0.46*****	0.14				
P-VAS	-0.02	-0.08	**0.30***	-0.05	-0.01	0.28			
EQ-5D-VAS	0.04'	0.16	-0.21	-0.31	-0.10	-0.11	-0.40		
PCS	-0.14	-0.11	-0.19	-0.19	**-0.34***	-0.08	**-0.47****	**0.66*****	
MCS	0.024	0.03	-0.15	-0.07	0.02	-0.20	-0.02	**0.30***	0.06

Abbreviations
SLAM: Systemic Lupus Activity Measure.
SLEDAI: SLE Disease Activity Index.
SLICC: the Systemic Lupus International Collaborating Clinics Damage Index
MD-VAS: Physician Visual Analogue Scale of disease activity; P-VAS: Patient Visual Analogue Scale of disease activity.
PCS: SF-36 Mental component score; PCS: SF-36 Physical component score.
Bold values indicate significant correlations: * p<0.05 ** p< 0.01 *** p< 0.001 ****p<=0.0001

APPENDIX F

Table F Variability (SD) in Measure of Disease Activity and Damage

APPENDIX E

Table E 1 Variability (SD) in Measure of Disease Activity and Damage

Disease Activity	Our study	Fortin's study	Others' study
SLAM	4.1	4.8	6.5*
SLEDAI	5.8	6.4	5.2 **
MD-VAS	1.4	2.0	
P-VAS	2.3	2.3	
SLICC	2.8	1.6	1.1**,

Abbreviations
SLAM: Systemic Lupus Activity Measure.
SLEDAI: SLE Disease Activity Index.
SLICC: the Systemic Lupus International Collaborating Clinics Damage Index
MD-VAS: Physician Visual Analogue Scale of disease activity.
P-VAS: Patient Visual Analogue Scale of disease activity.
* From Burckhardt study,; ** from Hanly study;

APPENDIX G

Figure G: Plots to Verify Assuptions of Multiple Linear Regressions

APPENDIX G

Figure G. 1 Plot of Residual vs Predicted Values of EQ-5D VAS From the Multiple Linear Regression Model

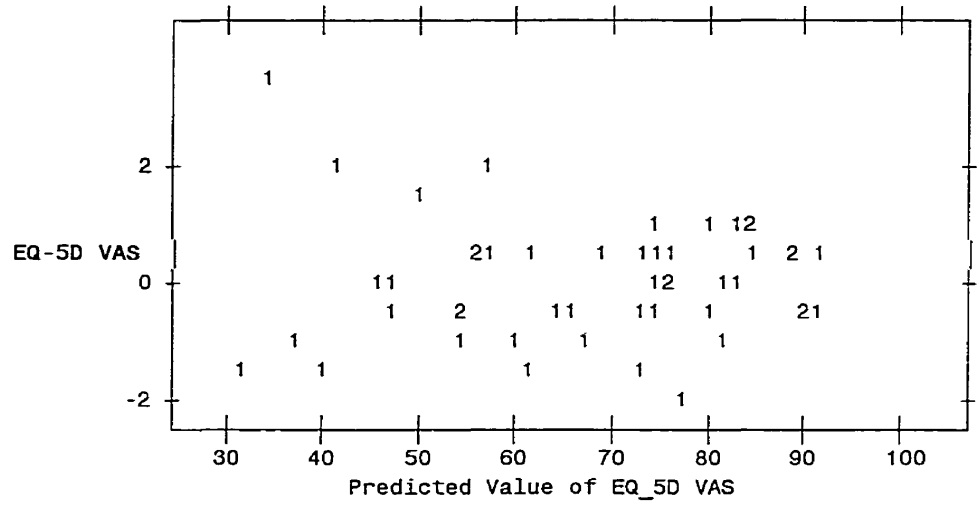


Figure G. 2 **Plot of Residual vs Predicted Values of PCS and MCS From the Multiple Linear Regression Model**

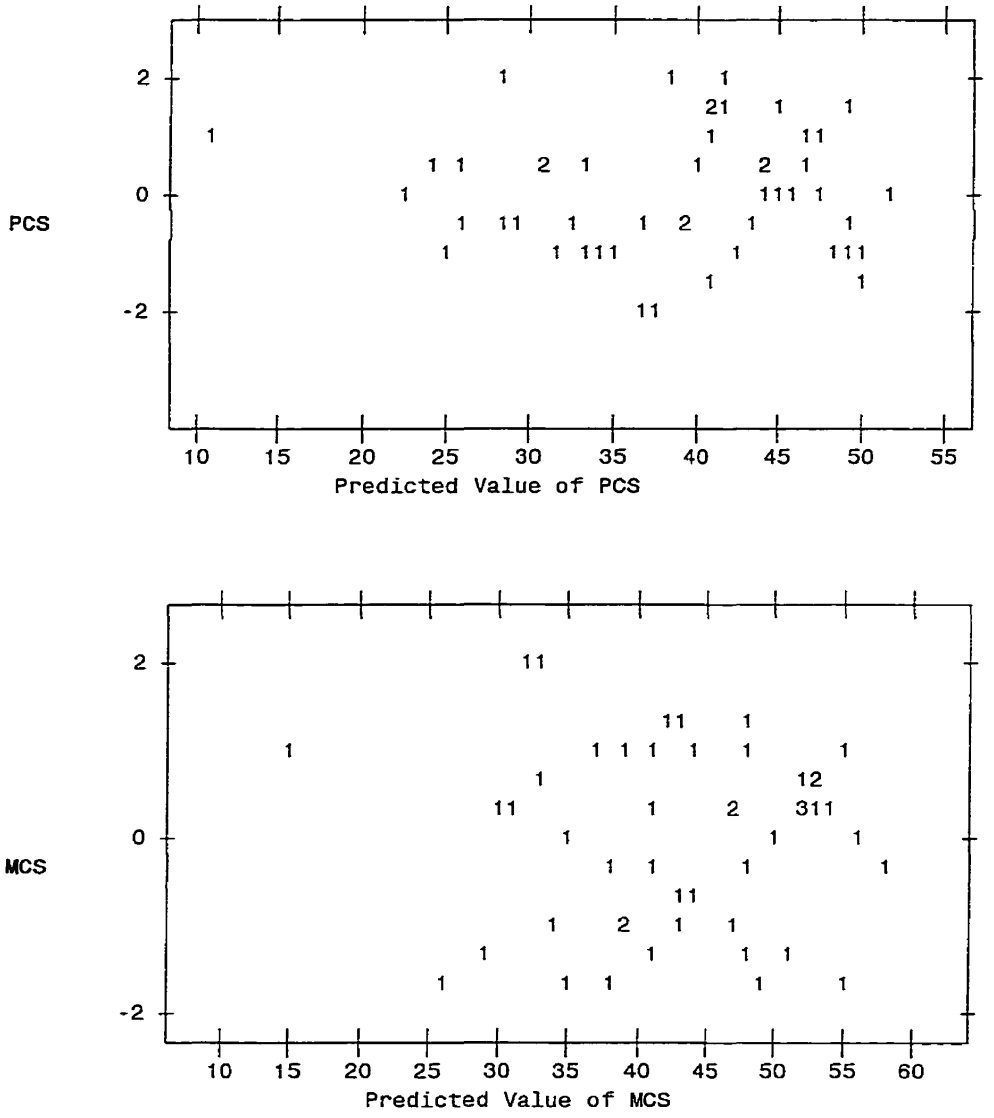


Figure G. 3 Plot of Residual vs Predicted Values of Physical Function and Role Physical From the Multiple Linear Regression Model

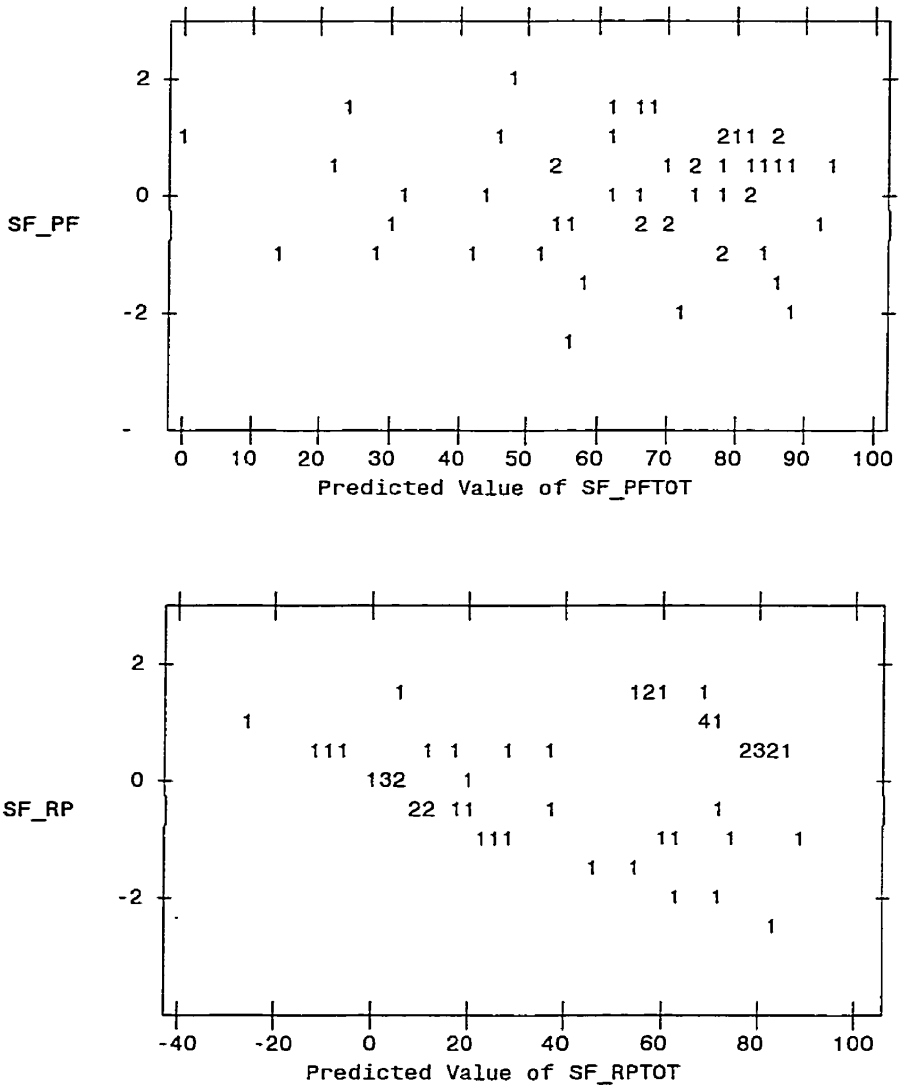


Figure G. 4 Plot of Residual vs Predicted Values of Bodily Pain and General Health From the Multiple Linear Regression Model

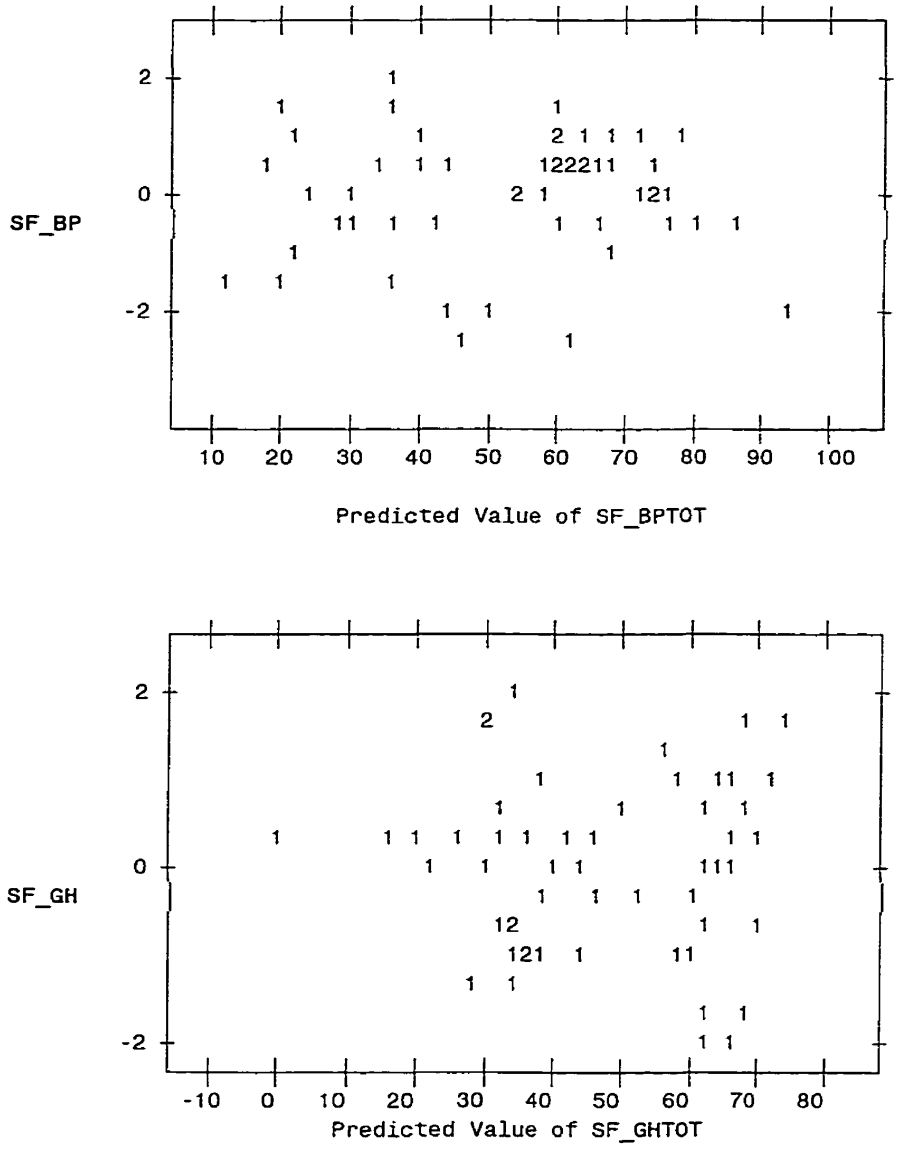


Figure G. 5 Plot of Residual vs Predicted Values of Vitality and Social Functioning From the Multiple Linear Regression Model

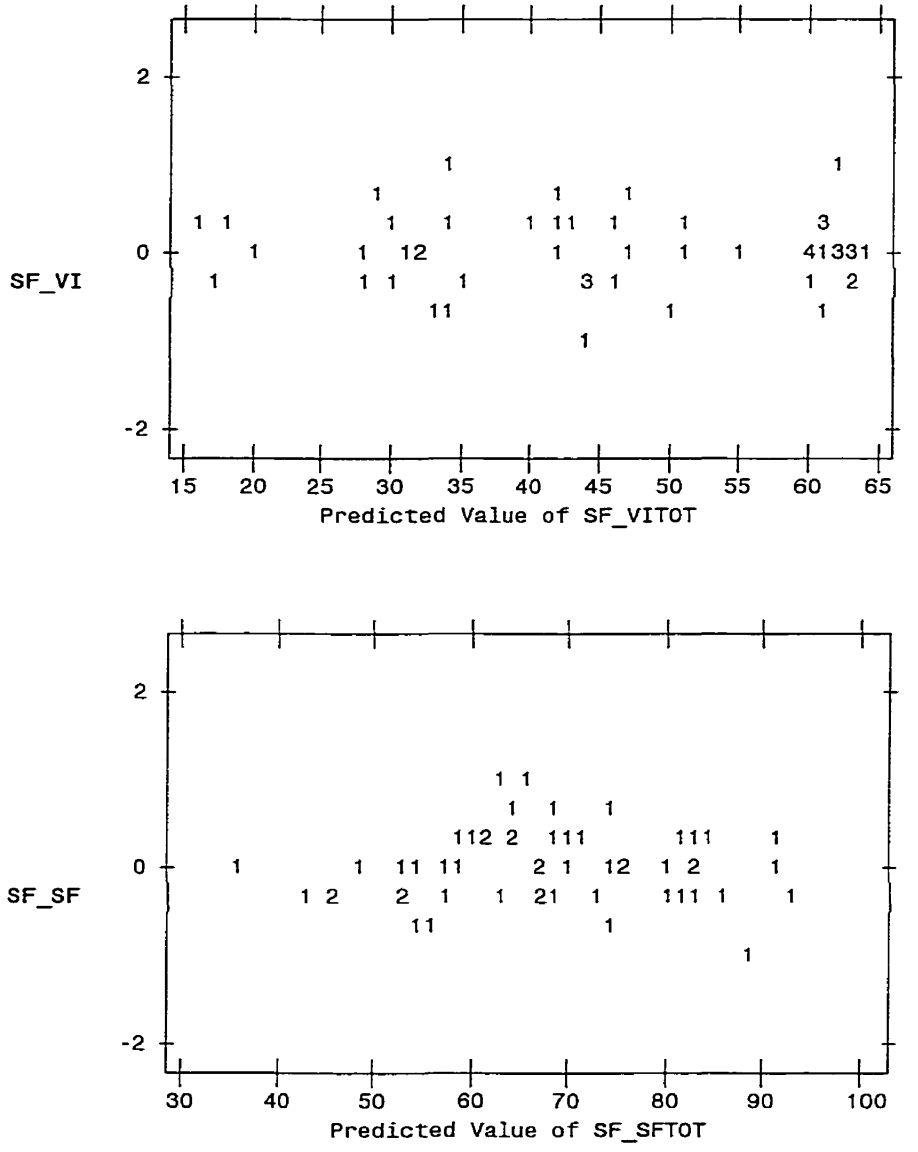


Figure G. 6 Plot of Residual vs Predicted Values of Role Emotional and Mental Health From the Multiple Linear Regression Model