

QUALITY OF LIFE IN MULTIPLE SCLEROSIS

Marjorie Bowman, RN, BScN

School of Nursing

Faculty of Health Sciences

University of Ottawa

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“A goal is a dream with a deadline”.

Napoleon Hill

Thesis Abstract

Objective: To explore quality of life in patients with multiple sclerosis.

Concept Analysis: A concept analysis of quality of life in multiple sclerosis was conducted using Rodgers' evolutionary concept analysis method. Eighty-three studies were reviewed.

Study Proposal for Secondary Analysis: The proposal was for a secondary analysis using a quantitative, longitudinal, repeated measures design to determine if stem cell transplant has an impact on the quality of life of multiple sclerosis patients with aggressive disease.

Summary of Findings: A concept analysis provided valuable insight into the use and understanding of the concept of quality of life in the multiple sclerosis literature. The subjective and multidimensional attributes of quality of life in multiple sclerosis were similar to findings in previous concept analyses of quality of life in general and in other diseases. The other attributes of the concept being measureable, modifiable and predictable revealed the uniqueness of quality of life in multiple sclerosis and provided a foundation for the development of future research. The results of the secondary analysis will provide new knowledge of a novel treatment for multiple sclerosis and its impact on quality of life. This advancement of knowledge in nursing and across health care disciplines will aid in the delivery of collaborative and comprehensive patient-centred care to ultimately improve the lives of multiple sclerosis patients.

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years of my nursing career. They are the real heroes in helping us to understand and research this disease and to them I am immensely indebted. A few of the patients told me they wanted to write books about their struggles with MS and their journey through a stem cell transplant. One patient, Fiona Fifield, accomplished her goal and wrote her book “Fiona’s Fight” this year. Not only did she write it but she is donating a portion of the proceeds to the MS Society of Canada.

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List of Abbreviations

Abbreviation

MS	Multiple Sclerosis
QoL	Quality of Life
HRQoL	Health-Related Quality of Life
DMT	Disease Modifying Therapy
SCT	Stem Cell Transplant
PCORI	Patient-Centered Outcomes Research Institute
SPOR	Strategy for Patient-Oriented Research
PRO	Patient Reported Outcomes
EDSS	Expanded Disability Status Scale
APN	Advanced Practice Nurse

Chapter One

Introduction

Introduction

Multiple Sclerosis (MS) is a chronic, progressive, immune-mediated disease of the central nervous system with an unpredictable course (Compston & Coles, 2002). In Canada, approximately 100 per 100 000 individuals are afflicted with MS, which is amongst the highest prevalence of MS in the world (Evans et. al., 2013). MS affects women almost three times more often than men and is most commonly diagnosed between the ages of 20 and 40 (Miller & Allen, 2010; Orton et. al., 2006). Symptoms can include fatigue, visual disturbances, weakness, reduced mobility, bladder, bowel and sexual dysfunction, sensory problems, cognitive decline and emotional disturbances (Compston & Coles, 2008).

The three most common categories of MS are relapsing-remitting, secondary progressive, and primary progressive; however, aggressive MS is now recognized as a category of the disease requiring more aggressive treatment (Rush, MacLean & Freedman, 2015). A Canadian prospective database study of over 5000 MS patients found that between 4-14% of patients met the definition of aggressive MS, which is characterized by multiple relapses and rapid progression (Freedman, 2013; Menon, et. al., 2013). Poor outcomes are highly predictable in patients who experience numerous relapses in the first two years after the onset of MS, develop motor or balance deficits early on and have progression of disease instead of remission post relapses (Degenhardt, Ramagopalan, Scalfari & Eber, 2009).

Despite advances in treatments for MS and countless clinical trials studying new therapies, there is no cure for MS. The first disease modifying therapies (DMT's) for MS were developed in the 1990's (Interferon-beta, Glatiramer Acetate) and currently there are five injectable DMT's, three oral therapies and two intravenous monoclonal antibody therapies (Freedman, 2013). Numerous new therapies are being investigated in clinical trials including

new oral options, monoclonal antibodies and stem cell transplant (Vosoughi & Freedman, 2010). Current MS therapies have demonstrated only partial efficacy in controlling the disease and they have a variety of side effect profiles that on their own can add to the struggles of dealing with the disease (Vosoughi & Freedman, 2010). It is for these reasons that new therapies are being researched and developed for different types of MS including aggressive disease (Rush, et al, 2015). Treatment choices are becoming more complex and a full understanding of their impact on patients will help to provide the best treatment option for each patient (Freedman, 2013).

The primary outcomes of MS therapies traditionally focused on the number of relapses, physical disabilities or the number of new lesions identified through magnetic resonance imaging (MRI); however, MS patients reported that role limitations and cognitive and emotional problems were concerns that had as much as or even greater of an impact than physical symptoms or disability status (Eldar, 2003; Fernandez, Baumstarch-Barrau, Simeoni & Auquier, 2011; Mitchell, Benito-Leon, Gonzalez & Rivera-Navarro, 2005; O'Connor, Lee, Ng, Narayana & Wolinsky, 2001; Zwibel & Smrtka, 2011).

Stem Cell Transplant for Multiple Sclerosis

Stem cell transplant (SCT) has been proposed as a treatment for aggressive MS due to the inefficacy of traditional therapies. Worldwide, more than 600 patients with MS have been treated with SCT in primarily small, single centre, phase one or two non-randomized studies (Atkins, 2010; Atkins & Freedman, 2009; Saccardi et al., 2012). A substantial number of patients with aggressive forms of MS have experienced longstanding progressive resolution of disabilities following SCT, which is an outcome that differs from currently licensed treatments (Atkins, 2010).

A review of the literature on assessing quality of life (QoL) in MS patients having SCT suggests the assessment of QoL be included as a relevant evaluation of the impact of the treatment on the whole person to support objective clinical findings (Burt et al., 2009; Frodin, Borjeson, Lyth, Lotfi, 2011; Guimaraes, Oliveira-Cardoso, Mastropietro, Voltarelli, & Santos, 2010; Novik et al., 2005; Saccardi et al., 2005). The results from the literature show that SCT can improve patients QoL by halting further progression of the disease (Burt et. al., 2009; Frodin et. al., 2010; Guimaraes et. al., 2010; Novik et. al., 2005; Saccardi et. al., 2005; Shevchenko et. al., 2015).

Quality of Life in MS

The impact of MS on QoL has been well documented in healthcare literature for over 20 years (Amato et al., 2001; Benito-Leon, Morales, Rivera-Navarro & Mitchell, 2003; Fernandez et al., 2011; Lerdal, Gulowsen Celius & Moum, 2009; Somerset, Peters, Sharp & Campbell, 2003; Vickery, Hays, Harooni, Myers & Ellison, 1995). Over the past several years, the assessment of QoL as a patient-reported outcome in MS clinical trials has become increasingly popular (Fernandez, et al., 2011; Lerdal et al., 2009; Shaffler, et al., 2013). Studies show that patients with MS not only have significantly poorer QoL scores on all dimensions of a commonly used health survey compared to the general population, but also compared to patients with rheumatoid arthritis and inflammatory bowel disease (Riazi et al., 2003; Rudick, Miller, Clough, Gragg, & Farmer, 1992; Vickery, et al., 1995). MS had a much greater impact on QoL compared to the other chronic illness populations because MS is a chronic progressive disease with no cure that typically produces multiple distinct problems (eg. motor, sensory, visual, bowel and bladder, cognitive impairment and relapses) that are more disruptive to patient well-being (Baumstarck et al., 2013; Rudick, et al., 1992).

In May 2011, an International Conference on Disability Outcomes in MS was held in Washington, DC, USA. The committee recommended the assessment of patient-reported outcomes, such as QoL, in addition to clinician-assessed objective disability outcomes in clinical trials for MS (Cohen et al., 2012). Patient-reported outcomes can provide a valuable sense of the clinical effects of a treatment from patients' perspectives, including the trade-off between efficacy, practical issues and adverse effects (Cohen et al., 2012).

QoL assessments provide the patient's perspective on the overall effect of treatment, a better definition of a treatment success and an evaluation of any recovery of QoL which may be already highly compromised (Guimaraes et al., 2010; Novik et al, 2005; Saccardi et al, 2005). MS has a significant impact on QoL and it is important to ensure that it is not further compromised by aggressive treatments. Given that patients with aggressive MS are willing to take a higher degree of risk for the chance of disease stability and a better QoL, it behooves clinicians to ensure that QoL is not diminished by higher risk procedures (Parfenov, Schluep & Du Pasquier, 2013).

Concept of Quality of Life

In healthcare, the concept of QoL emerged after World War II in response to rapid advancement of technologies prolonging quantity of life (Plummer & Molzahn, 2009). By the 1970's, the perspective of the patient was beginning to be an important consideration in treatment outcomes and in the 1990's, QoL became a major concern in planning, implementing and evaluating healthcare and social policies (Harrison, Juniper & Mitchell-DiCenso, 1996). In a systematic review of concept analyses of QoL in nursing, Fulton, Miller & Otte (2012) describe QoL as a phenomenon central to nursing and to the human health experience. The authors

suggest that QoL is so foundational to nursing that it could replace health in nursing's metaparadigm of health, person, environment and nursing (Fulton et al., 2012).

Concept analysis is an approach used for knowledge synthesis of existing literature and several authors of previous concept analyses of QoL highlight the importance of developing a perspective of QoL that is unique to nursing, not based on the perspectives of sociology or other disciplines (Fulton et al, 2012; Hass, 1999; Mandzuk & McMillan, 2005; Meeberg, 1993; Plummer & Molzahn, 2009). Enhancing QoL is an important outcome for nursing interventions and nursing practice (Harrison et al., 1996; Hass, 1999). The challenge faced by nurses is to evaluate the effectiveness of interventions on QoL through advancement of the understanding of the concept and the use of effective measurements for QoL (Harrison et al, 1996).

QoL Conceptual Models and Frameworks

Two main conceptual models and frameworks guided and supported the research studies in this thesis. Parse's theory of human becoming moves nursing away from the traditional medical science-based practice to a human science focusing on the human being's experience of living and creating health (Parse, 1999). The goal is to enhance understanding of lived experiences of health. Parse's theory has been recommended by other nursing scholars as a framework for developing knowledge in nursing related to QoL. Parse defines QoL as "the individual's human view on living moment to moment as the changing patterns of shifting perspectives weave the fabric of life through the human-universe interconnectedness" (Parse, 1994, p.17). When using human becoming principles as a guide to nursing practice, nurses are present with people as they enhance their QoL (Parse, 1999). Parse acknowledges that the concept of QoL will always be essential in healthcare and improving it is the overarching goal of nursing (Parse, 1994; Parse, 2007; Plummer & Molzahn, 2009).

In 2005, Ferrans and colleagues developed the Conceptual Model of Health-Related Quality of Life (HRQoL) which is a revision of a conceptual model of patient outcomes originally developed by Wilson and Cleary in 1995 (Ferrans, Zerwic, Wilbur & Larson, 2005; Wilson & Cleary, 1995). The authors developed the new model based on their recognition that QoL research has increased in methodological rigor and sophistication in healthcare over the past 30 years, however, “progress has been hindered by the fact that the term “quality of life” has been used to mean a variety of different things, such as health status, physical functioning, symptoms, psychosocial adjustment, well-being, life satisfaction and happiness” (Ferrans, et al., 2005, p. 336). As a result, it became difficult to compare findings across studies or apply findings to practice (Ferrans, et al., 2005). The term “health-related QoL” was introduced to centre the focus on the impact of health, illness and treatment on QoL, as well as, to eliminate aspects believed not to be related to health such as cultural, political and societal attributes (Ferrans, et al., 2005). This framework provided the background and support to include both QoL and HRQoL as surrogate terms in the literature search based on their research that “a distinction between health-related and non-health-related QoL cannot always be clearly made” and they make reference to the fact that this is particularly true in chronic illness where “almost all areas of life are affected by health, and so become “health-related” (Ferrans, et al., 2005, p. 336).

Summary of Literature

QoL assessment has become increasingly popular and recommended in MS clinical trials. It is recognized by researchers and clinicians as a valuable measure for assessing overall health, evaluating treatment, managing care and is required to provide patient-centred care; however, QoL is inconsistently measured with a variety of assessment tools making it difficult to

understand and compare study result. New and more aggressive treatments are being studied in MS and the full impact of the treatments on patients must be completely understood. SCT is an aggressive treatment and the impact on QoL has been reported in a few studies with few patients with different treatment regimens, different lengths of follow-up and different assessment tools.

Justification for Studies

MS affects QoL but current literature has not analyzed the concept of QoL as it is unique to MS. A concept analysis is needed to provide valuable insight into the use and understanding of the concept in the MS literature and improve the comprehension of the impact of the disease on individuals. The results will provide new knowledge and a foundation for future QoL studies in MS. The secondary analysis proposal to study the QoL data captured in the Canadian MS/SCT study is needed to provide the impetus to study the results of the impact of aggressive MS on QoL before and after the treatment in a larger patient population with an MS specific QoL assessment tool.

Personal Impetus for this Thesis Research

The first patient in Canada to receive a stem cell transplant for multiple sclerosis underwent her treatment at The Ottawa Hospital in 2001. Between 2001 and 2009, 23 additional patients received transplants as part of a multi-centre clinical trial. As the research coordinator for the clinical trial, I was provided with an immensely valuable experience and I gained unprecedented knowledge as I met, supported and cared for each patient enrolled in the trial. I had the opportunity to interact with the patients, families, support networks and several interdisciplinary teams as the patients proceeded through each step of the transplant process and during the three year follow-up phase of the trial.

During this time, I also spoke to numerous MS patients who were interested in participating in the study but did not meet the inclusion/exclusion criteria. The conversations were difficult as patients clung to hope despite the risks and unknown outcomes of the treatment. I heard many personal reflections of lives affected by MS.

One of the secondary outcomes of the clinical trial was the assessment of QoL prior to transplant and every six months post-transplant for three years using a validated MS disease specific QoL questionnaire. Although I worked in the specialty of neuroscience nursing for eight years prior to coordinating the study, in that role I never saw a QoL tool or witnessed the formal evaluation of QoL. The questionnaire was also new to the patients and for some, completing it uncovered mixed emotions from relief that someone was interested in their QoL to sadness as they reflected on the questions and the impact MS was having on their lives.

As I began to better understand and reflect upon the life experiences of the patients before the study, during the experimental treatment and during follow-up, my interest in QoL for MS patients developed. I recognized the impact that MS had on all dimensions of their lives, on treatment decision making and on hope for a better QoL. I witnessed both the positive and negative experiences of the patients and their families, stimulating my desire to know more about QoL for all MS patients, hence the conception of the current research focus.

In my current role as Advanced Practice Nurse for MS and Neurology at The Ottawa Hospital, my goal is to share and implement the findings of my thesis for the care of all MS patients. The impact of MS on QoL has been well documented in healthcare literature over many years and according to Parse's nursing theory on human becoming, the concept of QoL will always be essential in healthcare (Benito-Leon, Morales, Rivera-Navarro & Mitchell, 2003; Parse, 1994; Parse, 2007). Researchers and clinicians now recognize the importance of QoL

outcomes as a measure for assessing overall health, evaluating treatment, and managing care; however, the assessment of QoL has not been implemented into clinical practice (Mitchell, et. al., 2005; Solari, 2005). New more aggressive treatments are available and being studied for MS and a whole understanding of a patient's experience will help to provide the best treatment option for each patient (Freedman, 2013).

Thesis Design and Objectives

The overall aim of this thesis was to explore QoL in patients with MS. The specific objectives were to: a) conduct a concept analysis on QoL in MS as it is used in the international literature; and b) develop a study proposal for a secondary analysis of the quantitative data collected in the Canadian MS/BMT study to determine whether stem cell transplantation changes the QoL over time for patients with aggressive MS. My thesis is comprised of five chapters:

- Chapter 1 provides a review of the literature related to the thesis objectives, states the problem and provides justification for the studies. As well, it describes my personal impetus for this thesis research and outlines the structure of the thesis chapters.

- Chapter 2 is a concept analysis that explores the concept of QoL in MS and synthesizes the evidence from the MS literature. It is structured as a manuscript and addresses the first objective of the thesis. This concept analysis was structured according to Rodgers' evolutionary method. The manuscript is formatted for and will be submitted to the Journal of Advanced Nursing.

- Chapter 3 is a research proposal for conducting a secondary analysis study and provides the context, background and methodology to be used to guide the analysis. This study proposal is included in my thesis because it was part of the impetus for the concept analysis and also

demonstrates the goal of concept analysis to use the results as a starting point for further inquiry rather than an end.

- Chapter 4 is a summary of my thesis findings and an integrated discussion highlighting its implications for nursing practice, education and research.
- Chapter 5 outlines the contributions of co-authors and acknowledgements.

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Chapter Two

Quality of Life in Multiple Sclerosis: A Concept Analysis

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Authors:

Marjorie Bowman, RN, BScN, MScN (candidate)
University of Ottawa, Faculty of Health Sciences
The Ottawa Hospital

Janet E. Squires, RN, PhD
University of Ottawa, Faculty of Health Sciences

Lisa Walker, PhD
The Ottawa Hospital, Department of Neuropsychology

Harold Atkins, MD, BMedSc., FRCPC
Physician, Ottawa Hospital Blood and Marrow Transplant Program.
Scientist, Center for Innovative Cancer Therapeutics, Ottawa Hospital Research Institute.
Associate Professor, Medicine, University of Ottawa

Dawn Stacey, RN, PhD
University of Ottawa, Faculty of Health Sciences

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Corresponding Author:

Marjorie Bowman, RN, BScN
The Ottawa Hospital
MS Clinic Box 606
501 Smyth Rd
Ottawa, ON
Canada
K1H 8L6
mbowman@toh.on.ca
Phone: 613 737-8532 x.1
Fax: 613 739-6631

Abstract

Background: Multiple sclerosis impacts the quality of life of people with the chronic, progressive disease. Quality of life is a concept frequently used in healthcare across and within diseases. Within multiple sclerosis, the understanding of quality of life is complex, often ambiguous or not well understood.

Objective: The overall aim was to explore the concept of quality of life as it relates to individuals living with multiple sclerosis.

Design: Rodgers' evolutionary concept analysis

Method: English language research literature published from 1986-2014 was reviewed and eligible papers were critically analyzed to explore the concept's antecedents, attributes and consequences. Surrogate terms, related concepts and an exemplar case were identified.

Results: Eighty-three papers were eligible. Health-related quality of life and patient reported outcomes were surrogate terms and related concepts were well-being, life satisfaction and functional status. Five attributes defined quality of life in multiple sclerosis: subjective, multidimensional, measurable, modifiable and predictable. The antecedents included patient and disease characteristics, interventions and treatments, development of measurement tools, multidisciplinary teams, and predictive factors of quality of life. The consequences were grouped into factors that optimize or diminish quality of life.

Conclusion: The findings help to situate the concept of quality of life into the current practice of multiple sclerosis care. The attributes of quality of life in multiple sclerosis being measurable, modifiable and predictable are new findings compared to previous concept analysis of quality of life in other diseases. The findings can be used to guide future research, enhance the care

provided by the multidisciplinary teams and maintain a patient-centered approach with a goal of improving quality of life for multiple sclerosis patients.

Introduction

Multiple Sclerosis (MS) and its treatments affect quality of life (QoL). MS is one of the world's most common neurological disorders with an estimated prevalence of 2.3 million people with MS worldwide (Browne, et al., 2014). MS is most commonly diagnosed between the ages of 20 and 40 during the peak productive years and it affects women three times more often than men (Orton et al., 2006; Solari, 2005). A diagnosis of MS threatens an unpredictable course of relapses, remissions and progression of disease (Compston & Coles, 2002). MS signs and symptoms vary depending on the affected regions of the central nervous system which can profoundly affect numerous aspects of everyday living, resulting in reduced QoL (Benedict et al., 2005; Forbes et al., 2006; Rudick & Miller, 2008; Russell et al., 2006; Twork et al., 2010). Studies show that patients with MS have significantly poorer QoL scores compared to the general population and notably lower QoL scores compared to patients with other chronic diseases such as rheumatoid arthritis, inflammatory bowel disease and Parkinson's (Miller & Allen, 2010; Riazi, et al, 2003; Rudick, et al., 1992; Vickrey, et al., 1995).

Researchers and clinicians recognize the importance of including QoL outcomes as a measure; however, QoL results from clinical trials in MS are not always published and QoL measures are underutilized in clinical practice (Baumstarck, et al., 2013; Mitchell, et al., 2005; Solari, 2005). National strategies for patient-oriented research, such as Patient-Centered Outcomes Research Institute (PCORI) in the United States and Strategy for Patient-Oriented Research (SPOR) in Canada are requiring studies to change the focus of research outcomes from traditional measures to outcomes of relevance to patients (CIHR, 2011; Frank, et al., 2014).

New and increasingly aggressive treatments are now available to MS patients and more are being investigated in clinical trials (Freedman, 2013; Tramacere, et al., 2015; Rio, et al.,

2011; Vosoughi & Freedman, 2010). Researchers and clinicians should strive to understand the full impact of the disease and its treatments on patients. To do so, patients' evaluations of their QoL must be incorporated into routine monitoring and in response to treatments (Baumstarck, et al., 2013; Yamout, et al., 2013). Understanding QoL in MS has been limited by narrow definitions, a focus on symptoms and little emphasis on the positive aspects of QoL (Hart, et al., 2005). The QoL in MS literature validates many different definitions, measures and interpretations of QoL, making it difficult to fully appreciate the concept in MS (Baumstarck, et al., 2013; Benito-Leon, et al., 2003).

Concept analyses have been completed on QoL in nursing and in diseases such as chronic obstructive pulmonary disease, lung cancer, end stage kidney disease, critical care patients and young people with chronic disease (Bond, 1996; Boudreau & Dube, 2014; Cooley, 1998; Fulton, et al., 2012; Mouser, 2014; Taylor, et al., 2008). A concept analysis of QoL in MS has not been done. A summary of the antecedents, attributes and consequences of QoL from previous concept analyses is outlined in Table 2.1. An overview of the previous concept analyses provided a greater understanding of the empirical knowledge on the concept of QoL and identified the following key findings. Concept analysis leads to a deeper meaning and recognition of the impact of a concept within clinical practice and can result in improved assessment and intervention on the part of patients and families (Mouser, 2014). Understanding the concept of QoL guides healthcare professionals to assist patients in the selection of treatment modalities most likely to be associated with a higher QoL (Boudreau & Dube, 2014). Concepts must be in constant revision to reflect changes in the healthcare system and the population's needs in an effort to maintain a client-centred approach to care (Boudreau & Dube, 2014).

Fulton et al's (2012) systematic review found the need for more robust and rigorous studies of the concept of QoL to explicitly explore the contextual elements of QoL as it is experienced by different groups of people. The objective of this analysis was to explore the concept of QoL as it relates specifically to individuals living with MS.

Method

Rodgers' method of evolutionary concept analysis was used to explore the concept of QoL in MS (Rodgers, 2000). Concept analysis is a fundamental step in conducting research to develop valuable knowledge and theories, facilitate communication to resolve conceptual confusion within disciplines and aid in the interpretation and application of research findings (Rodgers, 2000; Fulton et al., 2012). Rodgers' method is ideal for analyzing QoL in a chronic progressive disease, like MS, as it requires the attention of many healthcare disciplines and it is a prevalent, worldwide topic of research used since 1986.

The philosophical perspective of Rodgers' method is viewed as an inductive procedure to identify a consensus or "state of the art" of the concept and set a foundation for further research (Rodgers 2000, p. 97). The method maintains that concepts change over time and are influenced by the context in which they are used (Toftthagen & Fagerstrom, 2010). This differs from other concept analysis methods where the goal is to provide an operational definition of the concept (Walker & Avant, 2005; Wilson, 1963). According to Rodgers (2000), the identification of the attributes represents the primary accomplishment of concept analysis. Attributes identify the real definition of the concept by answering the questions, "What are the characteristics of the concept?" and "What is this 'thing' the writer is discussing?" (Rodgers, 2000. p.91). Any statements or ideas that provide answers to these questions establish data that is relevant to the concept's attributes (Rodgers, 2000).

Rodgers' iterative process is comprised of six primary activities: (1) identify the concept with its surrogate and related terms; (2) identify and select an appropriate realm for data collection; (3) collect data with focus on concept antecedents, attributes, consequences, context of concept use, interdisciplinary, sociocultural and temporal variations; (4) analyze data regarding the above characteristics of the concept; (5) present an exemplar case; and (6) identify implications for future development of the concept.

Data Collection Procedures

Search Strategy. A comprehensive review of the literature in PubMed, Medline, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane library, PsychINFO, EmBase and ProQuest databases was completed using the key words "quality of life" or "health related quality of life" and "multiple sclerosis" in the title or abstract in any healthcare discipline. Additional search filters included studies in humans, English only, and adults age 19 and older.

Screening Process. Titles and abstracts were reviewed based on selected inclusion/exclusion criteria (Table 2.2). The articles were considered in relation to the following inclusion criteria: 1) the words "quality of life" or "health related quality of life" and "multiple sclerosis" in the title or abstract; 2) citations identifying objectives and outcomes related to QoL or HRQoL in MS; 3) published and peer-reviewed citations from all disciplines without limitation on years of publication. Exclusion criteria were 1) languages other than English; 2) citations related to children and 3) theses, editorials, opinion articles. Articles meeting inclusion criteria or those where insufficient information to reach a decision had the full text examined. Eligible full articles were read and reviewed by the first author to discover data pertinent to the concept.

Data Extraction. Data collection in the Rodgers' evolutionary concept analysis method includes seeking data on the sociocultural, disciplinary and temporal variations of the concept, surrogate terms, related concepts, definitions and attributes, and antecedents and consequences (Rodgers, 2000). Key findings for each of the above data elements were extracted from each article. According to Rodgers, surrogate terms are a way of expressing the concept in words other than those chosen by the researcher (Rodgers, 2000). Based on a conceptual model of health-related QoL (HRQoL) developed by Ferrans and colleagues in 2005, it was decided that HRQoL would be included as a surrogate term and all QoL and HRQoL data would be included in this analysis (Ferrans, et al., 2005). Related concepts are concepts that are identified as having some similarities to the chosen concept but do not have all of the same attributes; however, identifying them can situate the concept into a broader knowledge base and provide more significance to the concept (Rodgers, 2000). Antecedents are defined as situations, events, or phenomena that directly precede an example of the concept while consequences are situations that follow an instance of the concept (Rodgers, 2000). Individual spreadsheets were created for the organization of data for attributes, antecedents, consequences, related concepts and references. Definitions of QoL and HRQoL used by the authors were collected along with QoL measurement tools and the QoL domains captured in the tools. Notes were kept to identify implications for nursing practice, education and research.

Synthesis of Analysis. Formal analysis started when data collection was complete. This phase of analysis is a process of continually organizing similar points in the literature until a cohesive, comprehensive and relevant system of descriptors is generated (Rodgers, 2000). The definitions, attributes, antecedents, consequences and measures were analyzed separately and organized in an inductive manner until major themes emerged. Common themes were organized

and word labels were selected or obtained directly from the data to provide clear descriptions for each element. The related concepts and surrogate terms were noted as short expressions rather than themes or phrases and a database allowed for their systematic analysis by calculating their frequency and identifying their common elements. A review of previous concept analyses of QoL in nursing and QoL in other diseases was done to compare and identify elements of QoL in MS that could distinguish it from the results of other analyses.

Results

Description of Sample

The primary search yielded 1235 citations (Figure 2.1). A total of 942 remained for screening after the removal of 293 duplicates. Subsequent to screening with inclusion/exclusion criteria, the full text of 89 articles was reviewed. A further six articles were excluded as they either did not fully meet the inclusion criteria or provide information to contribute to attributes of QoL in MS (Table 2.3). The final sample for the analysis included 83 articles.

Sociocultural, Disciplinary and Temporal Variations

The included articles were published from 1986 to 2014. Of the 83 articles, 29 (35%) of the studies were completed in North America, 25 (30%) in Europe, 12 (14%) in the UK, seven (8%) in the Middle East, three (4%) in Australia, one (1%) in Asia and one (1%) in South America. The remaining five (6%) studies were international collaborations with data collected from multiple countries.

Of the 83 articles, 21 (25%) represented a collaboration by multidisciplinary teams while others were discipline specific with 49 (59%) representing medicine, six (7%) from nursing, three (4%) from social work, and two (2%) from rehabilitation and psychology (2%). Multidisciplinary teams varied in their composition but included teams of physicians from

different specialties and/or nurses, social workers, psychologists, physiotherapists, occupational therapists, behavioural scientists, epidemiologists and health policy specialists.

Surrogate Terms and Related Concepts

HRQoL was the only surrogate term identified. Forty-six (55%) authors used QoL, 23 (28%) used HRQoL and 14 (17%) used both. The related concepts most commonly found in this analysis were well-being (n=38, 46%), life satisfaction (n=20, 24%), functional status (n=17, 21%) and patient-reported outcomes (PRO's) (n=3, 4%).

Definitions

Forty-five (54%) of the articles contained a definition of either QoL, HRQoL or defined both, while the remaining 38 (46%) provided data through statements, themes, QoL assessment tools or domains of QoL that contributed to the attributes of the concept. The domains of QoL are broader areas, dimensions or categories of symptoms or circumstances identified by patients and researchers as having influence on QoL, such as mobility, bowel and bladder function, cognitive function, emotional well-being and visual function (Gold et al, 2001, Vickrey et al., 1995). Thirteen definitions of both QoL and HRQoL were identified (Table 2.4). The definitions were related to QoL or HRQoL in general and no specific definition of QoL for MS was used.

Defining Attributes

The five defining attributes of QoL in MS were subjective, multidimensional, measureable, modifiable and predictable (Table 2.5).

Subjective. Of the 83 articles, 67 (82%) made reference to the subjectivity of QoL in MS (Table 2.5). The assessment of QoL in MS is subjective in that it arises from each individual's perception of one's life (Learmonth, et al., 2014). The full impact of the disease cannot be understood without the perception of the individual (Chruzander, et al., 2014; Miller & Dishon,

2006). Rothwell and colleagues (1997) studied how patients and clinicians perceived physical disability and concluded that patients were far less concerned about this aspect of their illness. The authors recognized the importance of different elements related to QoL, such as vitality, general health, mental health and treatment side effects; their impact on QoL and that patient opinion be considered when assessing treatment outcomes (Rothwell, et al., 1997).

Some symptoms of MS that negatively affect QoL, such as pain, fatigue and depression are subjective and can best be described by the patient (Benedict et al., 2005; Mitchell et al., 2005; Motl & McAuley, 2010). Opara et al. (2010) describe other subjective attributes of QoL impacting MS patients including perception of symptoms, level of fitness, self-image, satisfaction with family life, work, economic situation, interaction with other people, social support and life in general.

Multidimensional. Fifty-nine (72%) of the articles described multidimensional attributes of QoL in MS (Table 2.5). The understanding that MS impacts a person's life in many more ways than by physical disability alone was a common theme. The dimensions include but are not limited to at least three: physical, mental and social (Benito-Leon, et al., 2013; Forbes, et al., 2006; Goksel Karatepe, et al., 2011; Lobentanz, et al., 2004; Vickrey, et al., 1995). Until 1995, QoL in MS articles either addressed the medical/physical aspects of the disease or the emotional/social aspects then after 1995 the focus shifted to include the multidimensional aspects of the disease (Cella, et al., 1997; Vickrey, et al., 1995).

Miller and Allen (2010), from the disciplines of social work and psychiatry, describe QoL as all encompassing, including aspects of a person's environment, workplace conditions, and financial situation, regardless of severity of disease. Psychologists add past experience, adjustment to condition and future plans to the multidimensional attributes (Lintern et al., 2001).

Psychosocial well-being has been described as more important in terms of QoL in MS than physical function, which can be in conflict with the opinion of healthcare providers (Rothwell et al., 1997). Mitchell and colleagues (2005) view QoL as a multidimensional index of well-being: the sum of all sources of satisfaction minus all sources of worry from the patient's perspective.

Measureable. Fifty-nine (71%) of the articles included at least one measurement tool to assess QoL (Table 2.5). Fifteen different measurement tools (eight generic and seven MS specific) were used. Generic tools aid in the assessment of universal health concepts regardless of disease and provide comparisons across diseases or with healthy controls (Ozakbas, et al., 2007). The domains of the MS specific tools are outlined given their contribution to the concept (Table 2.6).

The first MS specific measurement tool, the MSQoL-54, was developed in 1995 (Vickrey, et al., 1995). Although the MS specific measurement tools were rigorously developed based on patient interviews and tested for validity and internal consistency, they do not capture all of the QoL domains in all citations identified in this review (Table 2.7). The most frequently cited domains of QoL assessment that are captured in the tools but also in citations not including tools are social function (n=45, 54%), emotional well-being (n=45, 54%), cognitive function (n=19, 23%), energy level/fatigue (n=19, 23%), pain (n=16, 19%) and mobility (n=16, 19%). Other QoL domains not assessed by the tools but that identify important considerations in the evaluation of QoL in MS are the availability of supports and resources (n=16, 19%), level of independence (n=12, 15%), economic/employment (n=6, 7%), health-promoting behaviours (n=4, 5%), spirituality (n=2, 2%) and culture (n=1, 1%).

Modifiable. Thirty-six (44%) of the articles described QoL in MS as modifiable (Table 2.5). As a result of QoL research and assessment, it is now recognized that several,

multidimensional determinants of health are associated with MS and if recognized are modifiable with the right interventions (Buchanan, et al., 2008; Fernandez, et al., 2011; Forbes, et al., 2006). The authors highlight that “interventions targeting specific outcomes will be more effective for those people with the targeted problem (e.g. pain, spasticity, incontinence, or memory and attention deficits)” (Kuspinar, et al., 2012. p.1702).

Forty-five (54%) of the articles discussed depression as a main modifiable factor influencing QoL (Amato, et al., 2001; Benedict, et al., 2005; Goksel Karatepe, et al., 2011; Lobentanz, et al., 2004; Patti, et al., 2003; Philips & Stuifbergen, 2008). Fatigue, pain, bowel, bladder and sexual dysfunction and cognitive impairment were other distressing yet modifiable factors identified that if treated can make a positive impact on QoL for individuals with MS (Amato, et al., 2001; Benedict, et al., 2005; Forbes, et al, 2006; Norvedt & Riise, 2003; Van Schependom, et al., 2014; Vickrey, et al., 1995).

Predictable. According to 32 (39%) of the articles, QoL in MS is also predictable (Table 2.5). The identified predictors can have either a negative or positive impact on QoL (Table 2.8). A literature review by Mitchell, et al., (2005) identified strong, moderate and weak predictors of reduced QoL with the strong predictors being depression, demoralization or hopelessness, cognitive impairment, lack of autonomy, lack of support and pain. The weak predictors were long duration of disease, neurological symptoms, subtypes of disease, forced unemployment and magnetic resonance imaging (MRI) disease burden which can be contrary to what many healthcare providers believe (Mitchell, et al., 2005). A 10-year follow-up population study found the degree of MS disability, depressive symptoms and cognitive impairment to be the worse predictors (Chruzander, et al., 2014).

Antecedents

The antecedents, attributes and consequences emerging from this analysis are summarized in Figure 2.2. Eight antecedents for QoL in MS were identified and include: the onset of MS symptoms or a diagnosis of MS; having the cognitive or functional ability to evaluate one's life; comprehensive assessment of the disease; clinical interventions and treatments for MS; development of tools to measure QoL; multidisciplinary healthcare providers/resources; empowerment of patients; and health-promoting behaviours (Russell et al, 2006). Receiving the diagnosis of MS has been described as “a major turning point in the life of a person” (Russell et al., 2006, p.66). The empowerment of patients to be active participants in their care, make treatment decisions and to have their ongoing experience with MS understood through patient-reported outcomes are antecedents to QoL in MS (Zwibel & Smrtka, 2011). Individual characteristics of the disease and their impact on patients, patient characteristics and personal ability to deal with MS also precede the concept (Turpin, et al., 2007).

The development of disease specific QoL measurement tools has facilitated the assessment of QoL in MS and is considered an antecedent. Multidisciplinary healthcare providers and resources; clinical interventions and treatments; and identification of predictors having negative or positive influence on QoL also emerged as antecedents (Kuspinar, et al., 2012; Mitchell, et al., 2005; Schwartz & Frohner, 2005; Somerset, et al., 2002). Stuifbergen et al. (2000) describe the severity of illness, barriers, resources, self-efficacy, acceptance and health promoting behaviours as other examples of antecedents.

Consequences

There are positive and negative consequences of QoL in MS. The positive consequences optimize QoL in MS and include: the possibility of a positive personal judgement of one's QoL;

an appreciation of patient priorities by patients themselves, family and healthcare providers; the ability to tailor and evaluate interventions; and promote shared decision making (Amato, et al., 2001; Lobentanz, et al., 2004; Mitchell et al., 2005; Miller, 1997; Miller & Allen, 2010; Reynolds & Prior, 2003; Solari, 2005).

The QoL of MS is affected by several predictors (Table 2.8) resulting in diminished QoL with possible consequences of depression, fatigue, unemployment, impaired physical function, cognitive impairment and social isolation (Amato, et al., 2001; Benedict, et al., 2005; Chruzander, et al., 2013; Turpin, et al., 2007; Yamout, et al., 2013). Diminished QoL alone, with confounding variables removed, has also been studied as a useful predictor of disability progression in MS (Benito-Leon, et al., 2013). Suicide is a consequence of poor QoL and the rate amongst people with MS was two to seven times that for the age-matched general population (Feinstein, 2011).

Evolution of Concept

The citations in the analysis covered a 28 year time period beginning in 1986 (Harper, et al., 1986) and represented several countries and different healthcare disciplines. The number of articles on QoL in MS has grown exponentially over three decades (Figure 2.3). The subjective and multidimensional attributes have been consistent over the years. The development and validation of disease specific QoL assessment tools beginning in 1995 have endorsed the measurement of QoL in MS from a patient perspective and have aided in the refinement of the multidimensional domains (Miller & Allen, 2010; Vickrey, et al, 1995). Multidisciplinary perspectives have led to a better understanding of the modifiable factors related to QoL in MS and provide support for a multidisciplinary collaborative approach to care (Benito-Leon, 2003; Miltenburger & Kobelt, 2002; Vitali, 2011). The positive predictors of QoL that were explored in

the MS research in the past five years offer strategies for healthcare providers to further understand and enable people with MS to achieve optimal QoL (Baumstarck et al, 2013; Benito-Leon et al., 2013; Chruzander et al, 2014; Yamout, et al., 2013).

The attributes of QoL in MS being measureable, modifiable and predictable differ from attributes identified in previous concept analyses and provide a foundation for the development of future research. Great strides were made in the development of measurement tools and the assessment of QoL is considered an ultimate endpoint of clinical interventions but its use in routine care of MS patients is still limited. Future research should incorporate a gold standard QoL instrument into the care process but not add to the chores of everyday practice (Solari, 2005). Concurrent attention to the efficacy of therapies and the modifiable factors identified through QoL assessment has the potential to positively change the impact of the disease (Fernandez, et al., 2011).

Exemplar Case

This exemplar case is used to provide a practical example of the concept of QoL in MS and to demonstrate the elements of the concept. Ms. J was diagnosed with MS at the age of 19. She was attending college, had a boyfriend and was physically active. Within five years of her diagnosis, she had five MS relapses, did not respond to two MS therapies and quit college due to overwhelming fatigue. A relapse at age 24 left her unable to walk or cut her own food. She required assistance with toileting and was admitted to a rehabilitation centre. Based on the Expanded Disability Status Score (EDSS) (Kurtzke, 1983) her score worsened by four points to a score of six out of 10 total and her MRI showed several new lesions on her brain and spinal cord.

Upon discharge from the rehabilitation centre, she was able to walk with a cane, her arm strength improved and she regained control of her bladder and bowel and EDSS improved by

one point. At that time, she was told she had aggressive MS and was provided with the opportunity to participate in an MS clinical trial using stem cell transplant. This experimental therapy had the potential to stop any further progression of her MS but also had a five percent mortality rate. This situation necessitated that she weigh her current QoL against the potential life-threatening risks of treatment for a better QoL. She shared her values and preferences with her family and her healthcare team. The assessment of her QoL before and after treatment provided valuable information to understand her perceptions of QoL, the impact of the treatment and the changes in her QoL. She has experienced a sustained improvement in her QoL since the treatment and has maintained an EDSS of 1.5 which demonstrate the modifiable attribute of QoL in MS.

Discussion

The objective of this concept analysis was to explore the concept of QoL in MS to provide a review of its current use, uncover the characteristics of the concept and build a foundation for further development and inquiry. Much like the hindrances that precipitated the development of the conceptual model of HRQoL by Ferrans and colleagues in 2005, the same can be identified in MS research. Their model was developed based on the authors' recognition that QoL research had increased in methodological rigor and sophistication in healthcare over the past 30 years, however, "progress has been hindered by the fact that the term QoL has been used to mean a variety of different things, such as health status, physical functioning, symptoms, psychosocial adjustment, well-being, life satisfaction and happiness" (Ferrans, et al., 2005, p. 336). As a result, it was difficult to compare findings across studies or apply findings to practice (Ferrans, et al., 2005). Despite the acknowledged need to consider QoL issues in MS, QoL

assessment remains underutilized and these issues should be explored and understood to promote the use of measuring QoL in MS clinical practice (Baumstarck, et al., 2013).

Comparison of the Concept of QoL in MS to QoL in Nursing and in Other Diseases

The subjective and multidimensional attributes of QoL in MS were similar to findings in previous concept analyses of QoL in nursing and in other diseases such as COPD, end stage renal disease, lung cancer and critical care (Table 2.1) (Bond, 1996; Boudreau & Dube, 2014; Cooley, 1998; Fulton, et al., 2012; Mouser, 2014; Taylor, et al., 2008). Subjective or patient derived data is now increasingly accepted as essential assessment domains in MS clinical research and treatment (Miller & Allen, 2010; Cohen et al., 2012). According to conclusions made by The National Quality of Life Project in the United States, conducted from 1987 to 1988, QoL for people with disabilities is made up of the same factors and relationships that were shown to be important to people without disabilities (Goode, 1994). The group stated that QoL “is experienced when a person's basic needs are met and when the person has the opportunity to pursue and achieve goals in major life settings” (Gulick, 1997). The fulfillment of basic needs and the achievement of goals point to the subjectivity of QoL as these will be unique to each individual person with MS.

The dimensions of QoL in MS include but extend beyond the commonly cited physical, mental and social domains. The multidimensional attributes of QoL found in the MS literature are not unlike the attributes described by Ferrans and colleagues (2005). Their domains include characteristics of the individual (demographic, developmental, psychological and biological factors), characteristics of the environment (social or physical factors) and their impact on five types of measures of patient outcomes including biological function, symptoms, functional status, general health perceptions and overall. It is imperative that healthcare providers understand the

multiple dimensions of MS in order to provide multidisciplinary interventions and support to enhance QoL (Jones, et al, 2013; Zwibel, 2009).

Numerous disease specific QoL measurement tools are available to clinicians and researchers. The development of the tools has provided valuable insight into the complexity of QoL in MS and how it can be measured (Miller & Allen, 2010). Disease specific tools are more sensitive than generic tools for detecting and quantifying small changes and are better able to distinguish QoL differences especially during the different phases of MS or during relapses and remissions (Baumstarck, et al., 2013, Ozakbas, et al., 2007). The abundance of tools has been considered a barrier to their usefulness and an internationally recognized tool would aid in the consistency of assessment and reported outcomes of QoL (Solari, 2005). Educational initiatives around QoL assessment should emphasize that the information obtained can provide a “valuable sense of the clinical effects of an intervention from patients’ perspectives, including the trade-off between efficacy, practical issues, and adverse effects” (Cohen, et al., 2012, p.471). The current disease specific tools assess the most commonly cited domains of QoL in MS including social function, emotional well-being, cognitive function and fatigue; however, other cited domains are not incorporated into assessment tools (Table 2.7). Support, resources, independence, employment, health-promoting behaviours, spirituality and culture are cited as additional determinants of QoL in MS not captured in current tools. These findings could lead to the development of a more refined QoL assessment tool to incorporate into clinical practice.

The current focus of the modifiable factors in MS revolves around disease modifying therapies. Currently, MS patients have 10 disease modifying therapies to choose from that have the potential to modify the course of the disease. Depression is the most common and

modifiable factor experienced by MS patients for which they should be carefully screened and provided treatment to help diminish its impact on QoL (Benedict, et al., 2005).

Given the complexity of MS and these modifiable factors, multidisciplinary teams and comprehensive disease management approaches have been recommended (Buchanan, et al., 2008). Nurses have a key role in assessing and maintaining QoL for those with chronic conditions and ultimately influence QoL through frequent interaction and continuity of care (Harrison, et al., 1996). Awareness of the factors that affect QoL can contribute to the nurses' ability to provide education, support and interventions to enhance the QoL in MS patients (Gulick, 1997; Tanriverdi, et al., 2010).

MS is identified as being an unpredictable, neurological disease; however, the current research on the predictors of QoL in MS provides hope that through assessment and discussions about QoL, changes can be made to the course of the disease. Knowing the predictors of QoL provides the opportunity to assess and meet previously unmet needs, predict previously unpredictable outcomes, and develop comprehensive interventions for favourable psychological and physical outcomes (Mitchell, et al., 2005). The positive predictors of QoL that were explored in the MS research offer strategies for healthcare providers to further understand and enable people with MS to achieve optimal QoL (Russel, et al., 2006; Stuijbergen, et al., 2000; Vitali, 2011). "Improving knowledge about the determinants of QoL and the potential predictive role of QoL on disability may reinforce the conviction of clinicians to use these measures in their MS clinical practice" (Baumstarck, et al., 2013, p. 3). Understanding the predictors or warning signs influencing QoL, identifying patients at risk for decline in QoL and intervening early can perhaps provide clinicians and patients with "the upper hand against a possible lifetime of declining HRQoL" (Turpin, et al., 2007, p. 1043).

The inclusion of the exemplar case provides a real life situation to illustrate the current status of the concept of QoL in MS. The high risk versus potential benefit ratio in this case of MS may be viewed as a limitation in illustrating the majority of MS cases but it recognizes the value of the QoL information for all involved in her circle of care. Treatment choices are becoming more complex and a full understanding of a patient's clinical condition will help to provide the best treatment option for each patient (Freedman, 2013).

Limitations and Strengths

A limitation of this concept analysis is that it included only English language publications leaving the possibility that some relevant publications may have been missed. Data sources were limited to peer-reviewed citations from electronic databases omitting popular media or lay literature. Rodgers (2000) states this type of literature may be beneficial in bridging the gap between the perspectives of providers and the recipients of care. A limitation of the methodology is that it doesn't take into account the quality of the research in the studies included. Another limitation was the analysis was completed by one person. Despite being completed by one person, the analysis was enhanced through auditing by two co-authors. The multidisciplinary analysis situates the concept across the wide spectrum of healthcare, which is a further strength of the analysis.

Conclusion

This concept analysis has revealed the essence of the concept of QoL in MS, provided insight into the evolution of the concept and established the foundation for further exploration of the concept. The assessment of the patient's perspective of QoL needs to become routine in the care of MS patients and future MS research.

Our findings help to situate the concept of QoL in MS into the current clinical practice of MS care. As treatment choices increase, difficult decisions with regards to treatment options and outcomes do as well. Our findings can be used to educate patients and healthcare providers, guide future research, enhance the care provided by the multidisciplinary teams, provide a foundation for the development of a refined QoL assessment tool and maintain a patient-centered approach with a goal of improving QoL for MS patients.

Tables and Figures

Table 2.1: Summary of Antecedents, Attributes and Consequences from Review of Concept Analyses of QoL in Nursing and Other Diseases

Reference	Antecedents	Attributes	Consequences
Systematic review of analyses of the concept of QoL in nursing (Fulton, et al 2012)	Person’s ability to perform self-evaluation	<ul style="list-style-type: none"> • Subjective (arising from individual perception) • Dynamic (amenable to change) • Multidimensional (having plurality of elements) • Value based (grounded in individual significance) • Interactive (able to be communicated and shared) • Contextual (grounded in circumstance) • Intangible (lacking physical indicators) • Health related (belonging to personal health status) 	Personal judgment of one’s QoL (satisfaction, happiness, well-being, self-esteem, dignity, independence, self-control, harmony, potential for self-actualization)
COPD (Mouser, 2014)	<p>Diagnosis of moderate to severe COPD</p> <p>Ability to evaluate one’s life, to identify the perception of QoL, to make a decision about one’s QoL</p>	<ul style="list-style-type: none"> • Subjective • Multidimensional • Dynamic • Achievement of goals or aspirations • Constraints of ill health and treatment 	<p>Negative - social isolation, dependency, depression, ineffective coping, dissatisfaction, and feelings of helplessness</p> <p>Positive - increased independence, social engagement, and satisfaction with and acceptance of one’s circumstances</p>
End Stage Renal Disease (Boudreau, 2014)	<p>Diagnosed with chronic kidney disease</p> <p>Individual's subjective definition of well-being in relation to the impact of the burden of disease on their physical, social, and psychological health</p>	<ul style="list-style-type: none"> • Ability to engage in vigorous activities • Ability to perform activities of daily living • Ability to engage in family, social, and occupational roles 	<p>Period of self-reflection to make decisions pertaining to treatment options and health-related outcomes</p> <p>Weigh the benefits and disadvantages of each treatment option against their own physical, emotional, social, and occupational dimensions of daily life</p>

<p>Young People with Chronic Illness (Taylor, et al, 2008)</p>	<p>Ability to make a decision</p> <p>Ability to evaluate one's life</p> <p>Develop ways of coping with their illness to get on with living</p>	<ul style="list-style-type: none"> • Subjective • Multidimensional • Dynamic • Achievement of goals or aspirations • Constraints of ill health and treatment 	<p>A continuum</p> <p>Poor perception - neither be satisfied nor accepting of their circumstance</p> <p>Risk-taking behaviour</p> <p>Positive perception – coping, adaptation and satisfaction with life</p>
<p>Lung Cancer (Cooley, 1998)</p>	<p>Ability to make a cognitive appraisal about his or her life</p> <p>Functional status, physical symptoms, emotional function, social function</p>	<ul style="list-style-type: none"> • Subjective experience • Multidimensional construct 	<p>Survival</p>
<p>Critical Care (Bond, 1996)</p>	<p>Differing notions of quality of life</p> <p>Cognitive ability to evaluate one's own life</p>	<p>Perception of a satisfactory state of social, emotional, physical, and mental health</p>	<p>An acceptable feeling of well-being despite physical limitations</p> <p>Objective evaluations of treatment outcomes</p> <p>Morbidity/mortality statistics</p> <p>Cost/benefit analyses</p> <p>Age studies performed in an attempt to determine QoL by persons other than the patient</p>

Table 2.2: Inclusion/Exclusion Criteria

	Included	Excluded
Participants	Adults 19 plus	Children
Design	<ul style="list-style-type: none"> • Randomized controlled trials • Non-randomized controlled trials • Quasi-experimental designs (cross-sectional, cohort, longitudinal, pre-post-test) • Qualitative studies • Systematic, narrative reviews 	<ul style="list-style-type: none"> • Theses • Editorials • Opinion articles
Objectives and Outcomes	Objectives and outcomes related to quality of life or health related quality of life in MS	Main theme, objective and outcomes not related to quality of life or health related quality of life in MS
Language	English	Other languages
Publication	<ul style="list-style-type: none"> • Published • Peer-reviewed • All available (no limitation on discipline or year) 	<ul style="list-style-type: none"> • Non-published • Not peer-reviewed

Figure 2.1: PRISMA Flow Diagram

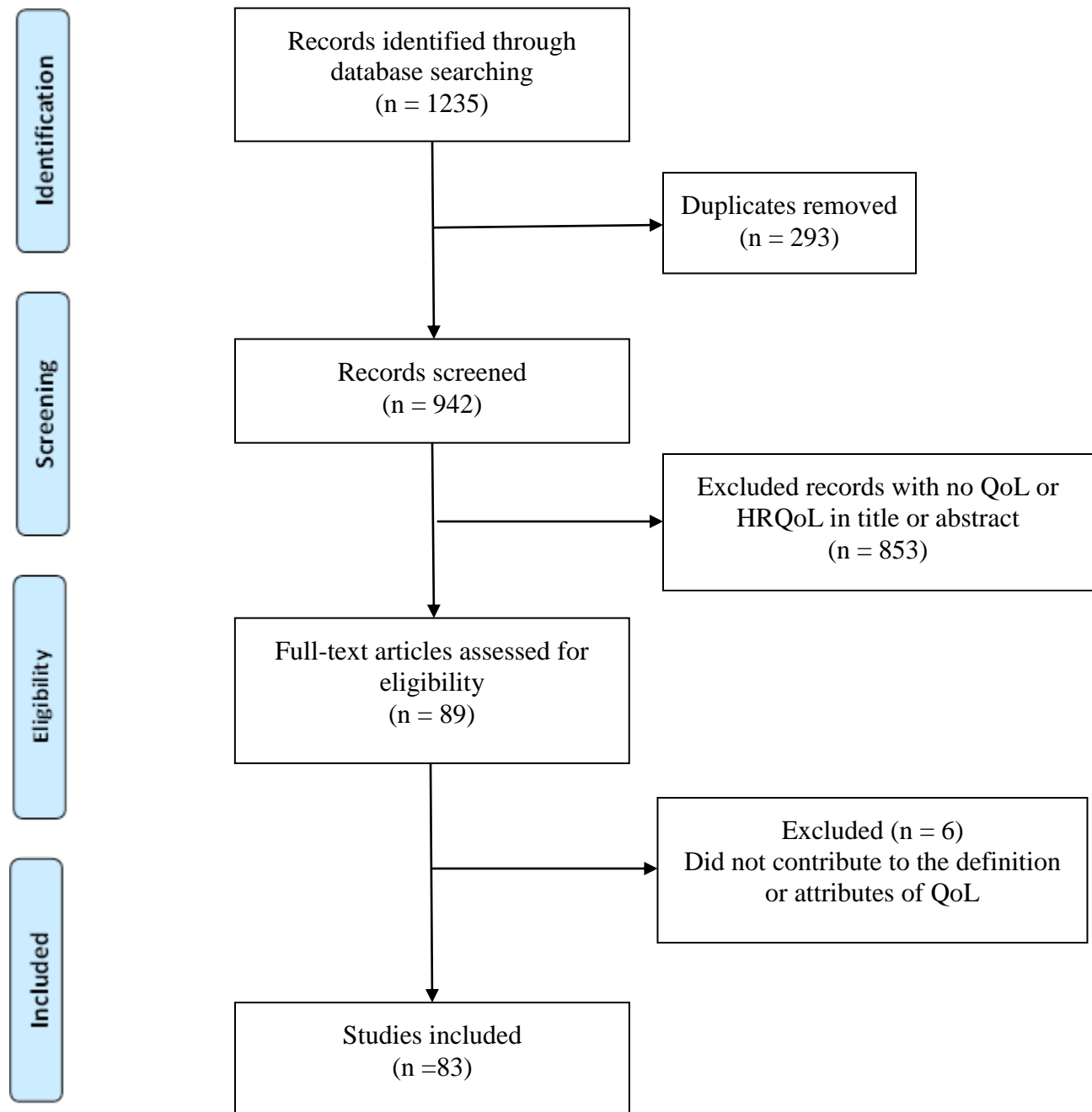


Table 2.3: Excluded Articles Based on Full Text (n=6)

Citation	Exclusion Reason
De Judicibus, M., & McCabe, M. P. (2007). The impact of the financial costs of multiple sclerosis on quality of life. <i>International Journal of Behavioral Medicine</i> , 14(1), 3-11.	Focuses on themes that are associated with financial changes due to the development of MS which include QoL but not main focus.
Goretti, B., Portaccio, E., Zipoli, V., Hakiki, B., Siracusa, G., Sorbi, S., & Amato, M. P. (2009). Coping strategies, psychological variables and their relationship with quality of life in multiple sclerosis. <i>Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology</i> , 30(1), 15-20.	Focuses on coping strategies, depression and anxiety but does not contribute to the definitions or attributes of QoL.
McCabe, M (2006). A Longitudinal Study of Coping Strategies and Quality of Life Among People with Multiple Sclerosis. <i>J Clin Psychol Med Settings</i> 13:369–379.	Focuses on coping strategies but does not contribute to the definitions or attributes of QoL.
Murphy, N., Confavreux, C., Haas, J., Konig, N., Rouillet, E., Sailer, M.,.....Merot, J. L. (1998). Quality of life in multiple sclerosis in France, Germany, and the United Kingdom. Cost of multiple sclerosis study group. <i>Journal of Neurology, Neurosurgery, and Psychiatry</i> , 65(4), 460-466.	Comparison of QoL across countries. Does not contribute to the definitions or attributes of QoL.
Nortvedt, M. W., Riise, T., Myhr, K. M., Landtblom, A. M., Bakke, A., & Nyland, H. I. (2001). Reduced quality of life among multiple sclerosis patients with sexual disturbance and bladder dysfunction. <i>Multiple Sclerosis</i> (Houndmills, Basingstoke, England), 7(4), 231-235.	Focuses on specific symptoms of MS and does not contribute to the definitions or attributes of QoL.
Wang, J.L., Reimer, M.A., Metz, L.M., Patten, S.B. (2000). Major Depression and Quality of Life in Individuals with Multiple Sclerosis. <i>International Journal of Psychiatry in Medicine</i> ; 30, 4; 309-317.	This article focuses on major depression and does not contribute to the definitions or attributes of QoL.

Table 2.4: Definitions of QoL and HRQoL

Definition of QoL	Reference
A term used in contemporary social science to refer to a person’s subjective sense of well-being or satisfaction with important areas of life.	Cella et al, 1996 (Cited by Benito-Leon et al, 2003; Gulick, 1997; Goksel Karatepe et al, 2011; Morales-Gonzales et al, 2004; Schwartz & Frohner, 2005; Stuifbergen et al, 2000)
The individual’s perceptions of their position in life in the context of the culture and value system in which they live, and in relationship to their goals, expectations, standards, and concerns.	WHO, 1995 (Cited by McCabe & McKern, 2002; Mitchell, et al, 2005; Rudick & Miller, 2008)
A multidimensional construct including physical, psychological and social functioning.	Gold et al, 2001 (Cited by Opara et al, 2010)
Satisfaction with one's key psychosocial life areas; a general sense of physical and psychological well-being; and the extent to which one is able to function in his or her role, has emotional and social support, and is free from emotional distress.	Koch et al, 2001
Quality of life is not a static, quantifiable construct; rather, it is highly subjective and is experienced as a continuous flow.	Somerset et al, 2003
It embraces all aspects of well-being and includes social, emotional, economic and cultural facets of our lives.	Benito-Leon et al, 2003
A generic concept reflecting concern with the modification and enhancement of life attributes, e.g., physical, political, moral and social environment; the overall condition of a human life (Medline, 1977).	Nortvedt & Riise, 2003
A multi-dimensional construct made up of life attitudes necessary for positive functioning.	Hart et al, 2005
A subjective and multidimensional concept. Its meaning depends on the theoretical perspective and the context in which it is used. While intending to measure QoL, many researchers are in reality measuring different aspects of health status.	Isaksson et al, 2005
A subjective measure of a patient’s life satisfaction that is affected by mood, coping mechanisms, life experiences, and emotional support as well as disease state	Zwibel & Smrtka 2011

A multidimensional measure, at the core of which is the extent to which the individual's hopes and ambitions are matched by experience.	Alshubaili et al, 2008
All-encompassing, including aspects of a person's environment, workplace conditions, and financial situation, regardless of disease.	Miller & Allen, 2010
Positive psychological well-being, vitality, life satisfaction, positive affect and optimism and physical health, psychological health, social relationships and environment.	Vitali, 2011
Definition of HRQoL	Reference
The value one places on current abilities and limitations, including the effects of illness and treatment upon physical, and emotional, and social wellbeing.	Cella et al, 1996 (Cited by Nicholl et al, 2001; Opara et al, 2010)
An individual's assessment of how a health problem and its treatment affect his/her ability to perform activities and roles that s/he values.	Fischer et al, 1999
QoL is a multidimensional construct, disagreement remains regarding the aspects of life which should be measured and the way in which it should be done. The literature demonstrates recognition of QoL as a subjective concept and as a result, self-rating measures (designed to elicit the patient's perspective) are now more commonly used.	Lintern et al, 2001
An individual's assessment of how a health problem affects his/her expected physical, psychological, and social/role functioning. It is a multidimensional construct that attempts to capture the patient's perspective on the physical, mental, and social aspects of health.	Shawaryn et al, 2002
Conceptualized as those aspects of life quality or function which are influenced by health status.	Benito-Leon et al, 2003
The capacity to derive satisfaction from meaningful behavior despite disease.	Benedict et al, 2005
A multidimensional construct including aspects of life or function affected by health status, including physical health and symptoms, psychosocial factors, and psychiatric conditions.	Miltenburger & Kobelt, 2002 (Cited by Forbes et al, 2006; Buchanan et al, 2008)
A subjective perception of health, is related to various symptom clusters in chronic illnesses.	Lerdal et al, 2008
The perception of the limitations that the diseases place on the experience of subjective QoL.	Alshubaili et al, 2008
The functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient	Rudick & Miller, 2008

<p>A multidimensional concept related to an individual's perception of their well-being and the level of their role fulfilment across a range of dimensions, including physical, psychological, social and symptom-related dimensions.</p>	<p>Vickrey et al, 1997 (Cited by Zwibel, 2009)</p>
<p>The biomedical and behavioral medicine position whereby functioning or physical health and well-being or mental health are two aspects of QoL that are influenced by health status.</p>	<p>Motl et al, 2008 (Cited by Learmonth et al, 2014)</p>
<p>Described and measured as a health profile which in pre-defined items emphasizes diverse aspects of HRQL for example the physical and the psychosocial aspects or as an index-score which is a summary score of predefined, either related or independent, items. In contrast to using predefined items, the person herself/himself can also define the concept of HRQL using a single global question.</p>	<p>Chruzander et al, 2014</p>

Table 2.5: Attributes of QoL in Multiple Sclerosis

Attribute	n= (of 83)	Example of Themes	References
Subjective	67 (82%)	<p>QoL is a subjective concept and as a result, self-rating measures designed to elicit the patient’s perspective, are commonly used (Lintern, 2001).</p> <p>Individuality, beliefs, personal circumstances and the course of the disease result in a complex and changing range of needs and preferences. QoL is not a static, quantifiable construct; it is highly subjective and is experienced as a continuous flow (Somerset, et al., 2002).</p> <p>QoL assessment should always be made by the patient and is hence always subjective (Miltenburger & Kobelt, 2002).</p> <p>The most desirable and reliable is the assessment by the patient himself, especially when the subjects of measurement are subjective aspects of QoL (Opara, 2010).</p>	<p>Alshubaili et al., 2008; Baumstarck et al, 2013; Baumstarck et al, 2013; Benito-Leon et al., 2013; Benito-Leon et al., 2002; Benito-Leon et al., 2003; Canadian group, 1998; Cella et al, 1996; Chruzander et al, 2014; Cohen et al, 2012; Devy et al, 2013; Fernandez et al, 2011; Fischer et al, 1999; Forbes et al, 2006; Ford et al, 2001; Ford et al, 2001; Goksel Karatepe et al, 2011; Gold et al, 2001; Gulick, 1997; Hopman et al, 2009; Isaksson et al, 2005; Jones et al, 2013; Kikuchi et al, 2011; Kistic Tepavcevic et al, 2013; Kuspinar et al, 2012; Learmonth et al, 2014; Lerdal et al, 2008; Lintern et al, 2001; Lobentanz et al, 2004; McCabe & McKern, 2002; Miller, 1997; Miller & Allen, 2010; Miller & Dishon, 2006; Miltenburger & Kobelt, 2002, Mitchell et al, 2005; Morales-Gonzales et al, 2004; Motl et al, 2008; Motl et al, 2010; Nicholl et al, 2001; Nortvedt et al, 2001; Nortvedt & Riise, 2003; O'Connor et al, 2001; Opara et al, 2010; Ozakbas et al, 2007; Patti et al, 2003; Pfenning et al, 1999; Phillips & Stuijbergen, 2008; Reynolds & Prior, 2003; Rothwell et al, 1997; Rudick et al, 1992; Rudick & Miller, 2008; Schwartz & Frohner, 2005; Shawaryn et al, 2002; Schaffler et al, 2013; Simeoni et al, 2008; Solari, 2005; Somerset et al, 2002; Stuijbergen et al, 2000; Turpin et al, 2007; Vasconcelos et al, 2010; Vickrey et al, 1995; Vickrey et al, 1997; Wu et al, 2007; Wynia et al, 2012; Yamout et al, 2013; Zwibel & Smrtka, 2011</p>
Multidimensional	59 (72%)	<p>Health-related QoL is a multidimensional concept related to an individual's perception of their general well-being and level of role fulfilment across a range of different physical, psychosocial and symptom-related phenomena (Miltenburger & Kobelt, 2002).</p> <p>Definitions of QoL are heterogeneous but a multidimensional construction is widely accepted (Lobentanz, et al, 2004).</p> <p>QoL is affected in a complex manner by the physical health, psychological status, social relationships, level of independence,</p>	<p>Alshubaili et al., 2008; Baumstarck et al, 2013; Benito-Leon et al., 2013; Benito-Leon et al., 2002; Benito-Leon et al., 2003; Buchanan et al, 2008; Cella et al, 1996; Chruzander et al, 2014; Cohen et al, 2012; Devy et al, 2013; Fernandez et al, 2011; Fischer et al, 1999; Forbes et al, 2006; Ford et al, 2001; Goksel Karatepe et al, 2011; Gold et al, 2001; Gulick, 1997; Harper et al, 1986; Hart et al, 2005; Hopman et al, 2009; Isaksson et al, 2005; Jones et al, 2013; Kikuchi et al, 2011; Kistic Tepavcevic et al, 2013; Koch et al, 2001; Lintern et al,</p>

		and self-beliefs of an individual as well as his or her interactions with his or her environment (Tanriverdi, et al., 2010).	2001; Lobentanz et al, 2004; Miller & Allen, 2010; Miltenburger & Kobelt, 2002; Mitchell et al, 2005; Motl et al, 2010; Nicholl et al, 2001; Nortvedt et al, 2001; Nortvedt & Riise, 2003; O'Connor et al, 2001; Opara et al, 2010; Ozakbas et al, 2007; Patti et al, 2003; Pfenning et al, 1999; Pittock et al, 2004; Reynolds & Prior, 2003; Rothwell et al, 1997; Rudick et al, 1992; Russel et al, 2006; Schaffler et al, 2013; Schwartz & Frohner, 2005; Shawaryn et al, 2002; Simeoni et al, 2008; Spain et al, 2007; Tanriverdi et al, 2010; Turpin et al, 2007; Van Schependom et al, 2014; Vasconcelos et al, 2010; Vickrey et al, 1995; Vitali, 2011; Wu et al, 2007; Yamout et al, 2013; Zwibel, 2009
Measurable	58 (71%)	<p>QoL measures reflect severity of disease, at least from the perspective of the afflicted individual (Rudick, et al., 1992).</p> <p>MS and its treatments have significant consequences on all aspects of life, from physiologic to daily function. The impact cannot be fully appreciated without assessment of the patient's well-being using QoL measures (Miller & Allen, 2010).</p> <p>A valid QoL measure refers to the extent to which a concept is well founded and corresponds accurately to the "real world" (Baumstarck, et al., 2013).</p>	Alshubaili et al., 2008; Baumstarck et al, 2013; Baumstarck et al, 2013; Benito-Leon et al., 2013 Benito-Leon et al., 2002; Benito-Leon et al., 2003; Buchanan et al, 2008; Cella et al, 1996; Chruzander et al, 2014; Cohen et al, 2012; Devy et al, 2013; Fernandez et al, 2011; Fischer et al, 1999; Forbes et al, 2006; Ford et al, 2001; Ford et al, 2001; Gold et al, 2001; Gulick, 1997; Hopman et al, 2009; Isaksson et al, 2005; Kikuchi et al, 2011; Kisic Tepavcevic et al, 2013; Koch et al, 2001; Kuspinar et al, 2012; Learmonth et al, 2014; Lerdal et al, 2008; Lintern et al, 2001; Lobentanz et al, 2004; McCabe & McKern, 2002; Miller & Dishon, 2006; Miltenburger & Kobelt, 2002; Mitchell et al, 2005; Motl et al, 2010; Nortvedt et al, 2001; Nortvedt & Riise, 2003; Ozakbas et al, 2007; Pfenning et al, 1999; Pittock et al, 2004; Rothwell et al, 1997; Rudick et al, 1992; Russel et al, 2006; Schaffler et al, 2013; Schwartz & Frohner, 2005; Shawaryn et al, 2002; Simeoni et al, 2008; Solari, 2005; Somerset et al, 2002; Somerset et al, 2003; Turpin et al, 2007; Van Schependom et al, 2014; Vasconcelos et al, 2010; Vickrey et al, 1995; Vickrey et al, 1997; Vitali, 2011; Wu et al, 2007; Wynia et al, 2012; Yamout et al, 2013; Zwibel & Smrtka, 2011
Modifiable	36 (44%)	Knowledge of which factors are determinants of HRQoL would assist clinicians in choosing the most appropriate interventions (Fernandez, et al., 2011).	Alshubaili et al., 2008; Benedict et al, 2005; Buchanan et al, 2008; Chruzander et al, 2014; Fernandez et al, 2011; Forbes et al, 2006; Fruehwald et al, 2001; Gulick, 1997; Hart et al,

		<p>Without such a comprehensive approach, the confounding due to unmeasured factors or their interdependence could not be avoided, and the identification of modifiable factors affecting QoL in patients with MS may remain elusive (Yamout, et al., 2013).</p>	<p>2005; Hopman et al, 2009; Isaksson et al, 2005; Kikuchi et al, 2011; Kuspinar et al, 2012; Lerdal et al, 2008; McCabe & McKern, 2002; Miller, 1997; Mitchell et al, 2005; Morales-Gonzales et al, 2004; Nortvedt et al, 2001; Nortvedt & Riise, 2003; Ozakbas et al, 2007; Patti et al, 2003; Phillips & Stuifbergen, 2008; Reynolds & Prior, 2003; Rudick et al, 1992; Rudick & Miller, 2008; Russel et al, 2006; Schwartz & Frohner, 2005; Shawaryn et al, 2002; Solari, 2005; Somerset et al, 2003; Tanriverdi et al, 2010; Wu et al, 2007; Wynia et al, 2012; Yamout et al, 2013</p>
<p>Predictable</p>	<p>32 (39%)</p>	<p>There is now considerable interest in understanding the predictors of HRQoL. Perhaps surprisingly, established physician rated measures of impairment and disability are not as closely linked with HRQoL as patient ratings of handicap and mood. Of particular note, depression has one of the strongest associations with low HRQoL (Benito-Leon, et al., 2003).</p> <p>Predictors of HRQoL reveal that both physical and psychological concerns are important and interact with each other. Psychological concerns and psychiatric complaints have long been overlooked and undertreated in MS (Mitchell, 2005).</p> <p>QoL instruments, in addition to traditional measures of clinical outcome, provide additional information and could be a part of a more comprehensive prediction of patient's prognosis (Kisic Tepavcevic et al, 2013).</p>	<p>Amato et al, 2001; Baumstarck et al, 2013; Benito-Leon et al., 2013; Benito-Leon et al., 2003; Chruzander et al, 2014; Ford et al, 2001; Gold et al, 2001; Gulick, 1997; Hopman, 2007; Hopman et al, 2009; Kisic Tepavcevic et al, 2013; Lerdal et al, 2008; Lobentanz et al, 2004; Miller & Allen, 2010; Mitchell et al., 2005; Morales-Gonzales et al, 2004; Motl et al, 2010; Nicholl et al, 2001; O'Connor et al, 2001; Phillips & Stuifbergen, 2008; Reynolds & Prior, 2003; Rothwell et al, 1997; Rudick & Miller, 2008; Russel et al, 2006; Somerset et al, 2002; Tanriverdi et al, 2010; Turpin et al, 2007; Vitali, 2011; Wynia et al, 2012; Yamout et al, 2013; Zwibel, 2009; Zwibel & Smrtka, 2011</p>

Table 2.6: MS Specific QoL Measures

	MSQoL-54 (Vickery, 1995)	FAMS (Cella, 1996)	MSQLI (Fischer, 1999)	MSIS-29 (Hobart, 2001)	LMSQoL (Ford, 2001)	HAQUAMS (Gold, 2001)	MusiQoL (Simeoni, 2008)	Domain Frequency, <i>n</i>
Citations, <i>n</i>	15	9	8	7	5	3	3	
Instrument items, <i>n</i>	54	59	138	29	8	38	31	
Core generic instrument	SF-36	FACT-28 items	SF-36					
MS Specific Domains								
Energy/Fatigue	✓*(1)	✓*(5)	✓*(21)	✓	✓	✓	✓	7
Social function	✓*(1)	✓*(7)	✓*(18)	✓	✓	✓	✓	7
Emotional Well-being/ Mood	✓	✓*(7)	✓*(18)	✓	✓	✓	✓	7
Cognitive function/ Thinking	✓*(4)	✓*(4)	✓*(20)	✓		✓	✓	6
Mobility		✓		✓	✓		✓	4
Health distress	✓*(4)				✓	✓		3
Sexual function	✓*(5)	✓*(1)	✓*(4)			✓		4
Symptoms				✓		✓		2
Bowel/bladder function		✓*(2)	✓*(9)	✓		✓		4
Visual function			✓*(5)			✓	✓	3
Pain	✓*(1)	✓*(4)	✓*(6)					3
Overall QoL	✓*(2)	✓						2
Self-confidence					✓			1
Domains Captured in Instrument, <i>n</i>	8	9	8	7	6	9	6	

* MS specific questions added to generic instrument, n (MSQoL-54=Multiple Sclerosis Quality of Life Instrument; FAMS=Functional Assessment of Multiple Sclerosis; MSQLI=MS Quality of Life Inventory; MSIS=MS Impact Scale; LMSQoL=Leeds MSQoL scale; HAQUAMS=Hamburg QoL Questionnaire in MS; MusiQoL=Multiple Sclerosis International Quality of Life questionnaire

Table 2.7: MS QoL Domains in the MS Literature

MS Specific QoL Domains in Citations and MS QoL Instruments	n=(of 83) Frequency
Social function	45 (54.2%)
Emotional Well-being/Mood	45 (54.2%)
Cognitive function/ thinking	19 (22.9%)
Energy/Fatigue	19 (22.9%)
Pain	16 (19.3%)
Mobility	16 (19.3%)
Sexual function	9 (10.8%)
Overall QoL	9 (10.8%)
Symptoms	8 (9.6%)
Bowel/bladder function	7 (8.4%)
Visual function	6 (7.2%)
Health distress	5 (6.0%)
Self-confidence	4 (4.8%)
MS Specific QoL Domains in Citations Not Captured in MS QoL Instruments	n=(of 83)
Support/resources	16 (19.3%)
Independence	12 (14.5%)
Economic/employment	6 (7.2%)
Health-promoting behaviours	4 (4.8%)
Spirituality	2 (2.4%)
Culture	1 (1.2%)

Table 2.8: Predictors of QoL in MS

Predictors of Positive Influence on QoL	n= (of 32)
MS education	15 (52%)
Employment	13 (45%)
Support	11 (38%)
Higher level of education	8 (28%)
Acceptance of disease	7 (24%)
Independence	6 (21%)
Social function	4 (14%)
Religiosity	3 (10%)
Interdisciplinary healthcare team	3 (10%)
Health promoting behaviours	3 (10%)
Intimacy	2 (7%)
Resilience	2 (7%)
Coping skills	2 (7%)
Self-esteem	1 (3%)
Predictors of Negative Influence on QoL	n= (of 32)
Depression	22 (76%)
Fatigue	15 (52%)
Pain/sensory symptoms	13 (45%)
Unemployment	13 (45%)
Physical function	12 (41%)
Lack of support	11 (38%)
Treatment side effects	11 (38%)
Low level of education	8 (28%)
Cognitive Impairment	7 (24%)
Duration of disease	5 (17%)
Disease progression	3 (10%)
Number of relapses	2 (7%)

Figure 2.2: Concept of Quality of Life in Multiple Sclerosis

Antecedents

- Onset of MS symptoms/diagnosis of MS
- MS patient’s ability to evaluate QoL
- Comprehensive assessment of characteristics and impact of disease
- Clinical interventions and treatments for MS
- Development of tools to measure QoL
- Multidisciplinary healthcare providers/resources
- Empowerment of patients
- Health-promoting behaviours

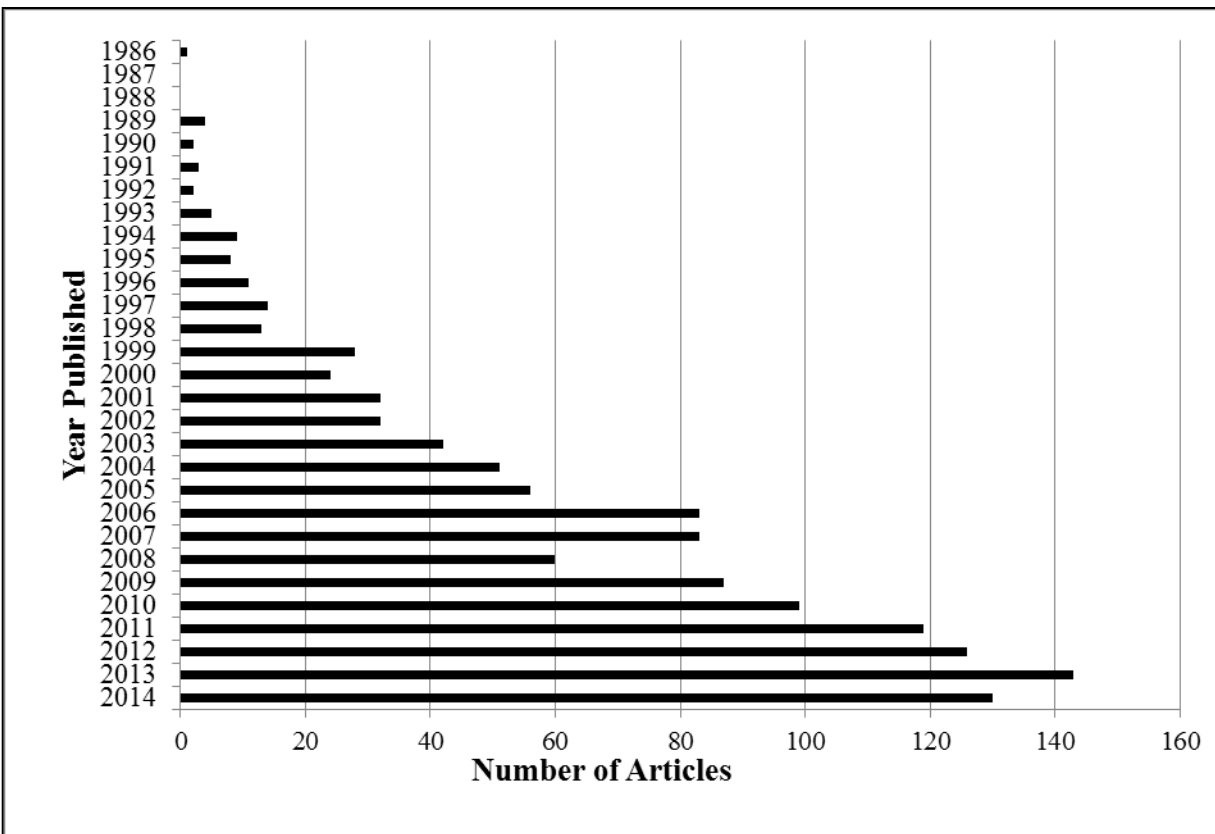
Attributes

- Subjective
 - patient’s perspective
- Multidimensional
 - beyond physical, mental and social
- Measureable
 - 14 MS QoL measurement tools
 - Interview
- Modifiable
 - Multidisciplinary interventions
 - DMT’s, new and emerging treatments
 - Symptom management/treatment
- Predictable
 - Identification of predictive factors having positive or negative or influence on QoL

Consequences

- Optimal QoL**
 - Positive personal judgement of one’s QoL
 - Appreciation of patient priorities
 - Tailor and evaluate interventions
 - Promote shared decision making
- Diminished QoL**
 - Depression
 - Fatigue
 - Unemployment
 - Impaired physical function
 - Cognitive Impairment
 - Social isolation
 - Disease progression
 - Suicide

Figure 2.3: PubMed-indexed Articles on QoL in MS



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Chapter Three

The Impact of Stem Cell Transplantation on Quality of Life for Patients with Aggressive Multiple Sclerosis

A Secondary Analysis Study Proposal

Abstract

Background: Quality of life assessment tools were completed by patients enrolled in a stem cell transplant study for aggressive multiple sclerosis.

Objective: To determine whether stem cell transplantation changes QoL over time for patients with aggressive multiple sclerosis.

Design: A secondary analysis will be utilized to examine the quantitative data using a longitudinal, repeated measures design.

Method: Twenty-three patients completed the self-administered MSQoL-54 questionnaire prior to transplant and every six months for three years post-transplant. The data analysis will include descriptive statistics to summarize sample characteristics and repeated measures analysis of variance will be used to test for statistical significance between three time points.

Relevance: This proposal demonstrates the goal of concept analysis to use the results as a starting point for further inquiry rather than an end. The results will provide insight into the impact of a novel treatment on QoL in MS.

Introduction

Stem cell transplant (SCT) is an aggressive treatment and the impact on quality of life (QoL) has been reported in a few studies with small numbers of patients with MS using different treatment regimens, different lengths of follow-up and different assessment tools (Burt et al., 2009; Frodin et al., 2011; Guimaraes et. al., 2010; Novik et. al., 2005; Saccardi et. al., 2005). SCT has resulted in significant improvements in the QoL of MS patients at one and two years post-transplant (Burt et. al., 2009; Guimaraes et. al., 2010; Saccardi et. al., 2005; Shevchenko et. al., 2015). Assessing QoL in MS patients having SCT is recommended to evaluate the full impact of the treatment (Burt et al., 2009; Frodin et al., 2011; Guimaraes et. al., 2010; Novik et. al., 2005; Saccardi et. al., 2005). QoL assessments provide the patient's perspective on the overall effect of the treatment, a definition of treatment success that is more meaningful to the patient, and an evaluation of any recovery of QoL which was already highly compromised (Guimaraes et. al., 2010; Novik, 2005; Saccardi, 2005).

MS has a significant impact on QoL and it must not be further compromised by aggressive treatments, however patients with aggressive MS are willing to take a higher degree of risk for the chance of disease stability and a better QoL (Parfenov et. al., 2013). An evaluation of the QoL data captured in the Canadian MS/SCT study will provide the results of the impact of aggressive MS on QoL before and after the treatment in a larger patient population with an MS specific QoL assessment tool.

Only three disease-specific QoL assessment tools were available when the primary study was designed 15 years ago. The MSQoL-54 was chosen as it was the most commonly used tool in MS clinical trials at the time and it is based upon the SF-36 generic QoL tool allowing for comparison of QoL results following SCT in other diseases (Vickery, et al., 1995).

Background

Primary Study

In 2001, the Canadian MS/Stem Cell Transplant (SCT) study began the enrolment of 24 patients with aggressive MS who underwent intensive chemotherapy to destroy their diseased immune system followed by a SCT of the patients' own purified stem cells to regenerate a new immune system (Atkins, 2010; Atkins & Freedman, 2009). The primary objective of the study was to establish whether or not the treatment could stop any further progression of the disease. The study included an evaluation of QoL prior to transplant and every six months post-transplant for three years. The enrolment ran over eight years between 2001-2009. The MSQoL-54 questionnaire was used to measure the impact of the experimental treatment on the QoL of patients involved in the trial.

The Canadian MS/SCT study is the only stem cell transplantation study for MS in Canada and it is officially titled: Targeting Multiple Sclerosis as an Autoimmune Disease with Intensive Immunoablative Therapy and Immunological Reconstitution: a potential curative therapy for patients with predicted poor prognosis MS. The study is a multi-centre, non-randomized, phase II efficacy study of the role of intensive immunosuppression on the natural history of MS. The sample size of 24 patients in the experimental arm was based on the restrictive eligibility criteria used to select patients and the intensive resources used for each transplant and disease activity monitoring required for each patient.

Theoretical Support

Ferrans and colleagues (2005) developed the Conceptual Model of Health- Related Quality of Life (HRQoL) based on their understanding that the term QoL was used as a catchall phrase for other concepts and it became difficult to compare findings across studies or apply

findings to practice (Ferrans, et. al., 2005). The authors explain that there is no clear distinction between health-related and non-health-related QoL particularly in chronic illnesses where all areas of can be affected. This model was used to guide the research plan for the secondary analysis of this study. More detailed definitions of the components of the model are included in Appendix A.

Objective

The overall aim of this proposed study is to determine whether stem cell transplantation changes the QoL over time for patients with aggressive MS.

Design

A secondary analysis will be utilized to examine the quantitative data collected from MSQoL-54 questionnaires using a longitudinal, repeated measures design and a self-administered questionnaire as the data collection tool. Secondary analysis involves the use of an existing data set to answer a new or different research question or hypothesis (Castle, 2003). Secondary analysis has become an increasingly popular nursing research method based on the benefits of cost effectiveness, efficiency, and convenience of data collection (Castle, 2003). Secondary analysis does have the disadvantage of requiring the researcher to work with an existing set of data and relinquishes control of the study population, the sample size and measures used for data collection (Castle, 2003; Polit & Beck, 2012; Windle, 2010). Longitudinal design is appropriate to use when researchers are assessing changes over time and often use repeated measures to evaluate short-term and long-term benefits or changes related to an intervention (Polit & Beck, 2012).

Methods

Participants

Participants for the secondary analysis study will include 23 (of the enrolled 24) patients from the Canadian MS/SCT study (Atkins & Freedman, 2009); one patient died one month post-transplant.

Inclusion criteria for the primary study included patients that:

1. Were considered to have a poor prognosis defined as a high probability of significant disease progression during the next 10 years.
2. Were between 18 and 50 years of age.
3. Had experienced multiple relapses soon after diagnosis and developed early sustained disability.
4. Had evidence of ongoing clinical MS activity despite at least one year of attempted treatment with approved immunomodulatory or immunosuppressive therapies.

Patients were excluded from the primary study if they had significant cardiac, renal, pulmonary or hepatic dysfunction, active infections, or other medical problems that would increase their risk of morbidity or mortality.

The Canadian MS/SCT study setting included in-patient and out-patient hospital encounters at three tertiary care hospitals in Ottawa, Montreal and Toronto. The participants were enrolled after obtaining informed consent, between February 2001 and April 2009, with six month follow-up measures occurring for three years ($n = 7$ time points/patient).

Procedures

A detailed outline of the SCT procedure was previously published (Atkins & Freedman, 2009). Patients completed stem cell mobilization and collection procedures followed by a ten day chemotherapy conditioning regimen and transplant of the collected cells. Patients were admitted to a stem cell transplant ward for supportive care. The average hospital stay was 39 days. Upon discharge from hospital, patients were closely followed with standard post-transplant practices and neurological evaluations based on the clinical trial visit schedule. Patients completed QoL questionnaires during clinic visits at baseline prior to any transplant related treatment and then every six months post-transplant for the three year follow-up duration of the study.

Measurement Instrument

The MSQoL-54 questionnaire (Appendix B) measures HRQoL (Vickery, et al., 1995). It was developed to construct a self-report measure of HRQoL for MS with the goal of combining the strengths of a generic measure with a disease-targeted approach. The MSQoL-54 combines the RAND 36-item Health Survey 1.0 (SF-36) with eighteen MS specific items. The MS specific items were constructed after a literature review and input from two MS physicians and a MS nurse specialist. The MSQoL-54 questionnaire has been translated into many languages and used in numerous clinical trials (Acquadro, Lafortune & Mear, 2003; Giordano, et. al., 2009; Solari, et. al., 1999). The questionnaire can usually be completed by patients with little or no assistance and takes about 15 minutes to complete. Patients with visual or writing difficulties were assisted by the research coordinator to complete the questionnaires. The questionnaire contains 54 items which generate 12 subscales, two summary scores and two single item measures. The 12 subscales are physical function, role limitations-physical, role limitations-emotional, pain, emotional well-being, energy, health perceptions, social function, cognitive

function, health distress, overall QoL and sexual function. The two summary scores are physical health composite and mental health composite while the single items are satisfaction with sexual function and change in health. The subscale scores are created by transforming the item scores linearly from 0-100 possible scores then averaging the item scores within subscales. The higher values indicate better quality of life (Appendix C).

The MSQoL-54 was tested for reliability and validity in the MS population (Vickery, et al., 1995). The questionnaire was sent out in 1993 to 231 adults with a diagnosis of definite MS. A response rate of 79% was obtained with 179 questionnaires returned. Internal consistency with Cronbach's alpha ranged from 0.75 to 0.96 for 12 subscales. A subset of 116 subjects was randomly chosen prior to the initial mail out to repeat the questionnaire to evaluate test-retest reliability which yielded a 94% response rate. The test-retest correlation coefficients ranged from 0.66 to 0.96 for 12 subscales. To evaluate construct validity, the researchers added self-report questions about disability which provided information comparable to information routinely obtained from the Expanded Disability Status Scale (EDSS), an assessment tool frequently used in MS clinical trials (Kurtzke, 1983). Questions were also included regarding sociodemographic data, hospitalization, comorbid medical conditions and help in questionnaire completion. The construct validity was supported by significant associations between MSQoL-54 scales and the answers to the self-report questions and EDSS. For example, significant associations occurred between the MSQoL-54 scales and the degree of MS symptom severity within the prior year, level of ambulation, employment limitations related to health, admission to hospital in the past year and depressive symptoms (Vickery, et al., 1995).

Data Analysis Plan

Descriptive statistics (eg. percentage for categorical data, means and standard deviations for interval and ratio data) will be used to summarize sample characteristics such as age, gender, previous treatments, type of MS, history of depression and family history. The MSQoL data for all seven time points for each patient enrolled in the study will be entered into a Microsoft Excel spreadsheet containing the MSQoL-54 scoring form (Appendix C). The data set will be examined for irregularities and missing values. The scores will then be entered into SPSS Version 22.0 to compute the means of the 12 subscale scores, the physical health composite score, mental health composite score, satisfaction with sexual function score and change in health score for each patient at each time point. The baseline, 12 month and 36 month time points will be chosen to evaluate the QoL at baseline prior to treatment, at 12 months (to obtain insight into the short-term impact of the treatment on QoL) and at 36 months (to observe the long-term impact of the treatment on QoL).

A repeated measures analysis of variance (RM-ANOVA) will be used to test for statistical significance between the three time points (Polit, 2010). The level of significance will be set at $\alpha = .05$. Significant results will be followed up with analyses of simple effects. Taking the small sample size into consideration, the data will also be interpreted by the non-parametric Friedman statistical test to evaluate the differences between results obtained in the selected time points (Pett, 1997).

Ethical Considerations

Ethical approval was obtained for the Canadian MS/SCT study from the institutional research ethics boards at The Ottawa Hospital, St. Michael's Hospital and McGill University

Health Centre prior to patient enrollment and was renewed yearly. The primary study continues to be renewed annually through the Ottawa Health Science Network Research Ethics Board.

An amendment to the primary study was submitted to the Ottawa Health Science Network Research Ethics Board (OHSN-REB) for the secondary analysis section of this project since the primary study was conducted at The Ottawa Hospital. Upon approval from OHSN-REB, reciprocal approval was obtained from the University of Ottawa Research Ethics Board (Appendices D and E). Permission has been obtained from the principal investigators of the primary study to access the MSQoL-54 questionnaires. Patients will not have to be re-consented for the secondary analysis. Patient confidentiality was maintained throughout the data collection process and only individual number codes will be used. The study files are stored in a locked office in The Ottawa Hospital MS Clinic at the General Campus and will only be accessed by the student, principal investigators and thesis supervisor. The electronic database will be password protected and stored within a secure drive at The Ottawa Hospital. Any data stored on portable devices will be protected with encrypted passwords. The collected data may be examined by the study investigator, the research supervisor and thesis committee. The study records will be stored for 15 years after study closure. Thereafter, electronic data will be deleted and study documents will be shredded.

Timeline

I will conduct the analysis over a six month time period with April 2016 as the anticipated start date (Table 3.1). Research ethics approval will be renewed for September 2016. The original data collection was completed in the primary study and the process of transferring the data for analysis has started. Table 3.1 highlights the research activities including data

preparation, data analysis, interpretation of data, preparation of reports and presentations followed by the research dissemination phase.

Table 3.1: Timeline for Secondary Analysis Activities

Month/Year	4/16	5/16	6/16	7/16	8/16	9/15
Data preparation						
Data analysis						
Interpretation of results						
Preparation of reports and presentations						
Dissemination						

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Chapter Four
Integrated Discussion

Thesis Summary

Introduction

The overall aim of this thesis was to explore QoL in patients with MS. An introduction and review of the literature was completed (Chapter 1) followed by a concept analysis of QoL in MS (Chapter 2) and a study proposal for a secondary analysis of QoL data collected in the Canadian MS/BMT study (Chapter 3). This chapter summarized the findings of these chapters, provided an integrated discussion of important considerations revealed through the development of this thesis, discussed implications for nursing practice with particular emphasis on the role of the advanced practice nurse and identified areas for further research.

Summary of Thesis Findings

The evolution of the concept of QoL in MS was analyzed from a multidisciplinary perspective in 83 articles published over 28 years. The analysis identified the “state of the art” of the concept and provided insight into current and emerging trends concerning QoL in MS. The findings from this thesis helped to situate the concept into the current clinical practice and research trends of MS care. The five attributes of the concept were identified as subjective, multidimensional, measureable, modifiable and predictable. The attributes, along with the antecedents and consequences of the concept, identified the duality of optimal versus diminished QoL in MS.

The proposal for a secondary analysis study to determine whether stem cell transplantation changes the QoL over time for patients with aggressive MS provided the background, objective, design, methods and data analysis plan for the study. Research ethics approval has been obtained for this analysis and approval was obtained from the investigators of the primary study to utilize this valuable data set. The treatment of aggressive MS is challenging

and the results of this proposed study will provide valuable research findings on the impact of a novel treatment on the QoL of this group of MS patients.

Lessons Learned From Thesis

Through the process of completing the previous chapters, three key considerations were recognized: a) an interdisciplinary/interprofessional collaboration approach to care would optimize QoL in MS, b) understanding QoL in MS can enhance patient engagement and shared decision-making, and c) the research findings related to QoL in MS need to be translated into practice.

Interdisciplinary/Interprofessional Collaboration. QoL is of interest to all healthcare disciplines involved in the care of MS patients. The multidimensional and modifiable attributes of QoL in MS identified in the concept analysis require an extensive scope of knowledge and interventions from a healthcare team (Fernandez, et al., 2011; Kuspinar, Rodriguez & Mayo, 2012). The terms multidisciplinary and interdisciplinary collaboration are often used interchangeably, however, there are subtle but important differences (Hanson & Spross, 2009). Multidisciplinary collaboration recognizes the importance of contributions of other disciplines while interdisciplinary collaboration recognizes the provision of comprehensive health services to patients by multiple disciplines, who work collaboratively to deliver quality care within and across settings (HealthForceOntario, 2007).

The majority of MS care is provided in outpatient clinics but within a hospital setting where collaboration with some disciplines is expedited. Due to current budget constraints in hospitals, collaboration with disciplines in other healthcare settings such as rehabilitation centres and in the community is now more common, making interdisciplinary collaboration more important to improve accessibility to valuable resources and provide safe, quality and cost-

effective care (Gallien, Gich, Sanchez-Dalmau & Feneberg, 2014). New MS therapies with higher risk profiles require the expertise of an even broader collaborative healthcare team (Rush, et al., 2015). The completion of the Canadian MS/SCT study was successful due to the work of a large interdisciplinary team and the collaboration resulted in improved QoL for many patients. The results of the secondary analysis will contribute to the knowledge supporting the impact of interdisciplinary collaboration in delivering quality care to MS patients.

Patient Engagement and Shared Decision-Making. Patient engagement is defined as actions individuals must take to obtain the greatest benefit from the healthcare services available to them (Reickmann, et al., 2015). The role of the patient is evolving from receiver to engager of healthcare while the role of healthcare providers must evolve from providers of healthcare to motivators and supporters of patients to achieve patient engagement (Reickmann, et al., 2015). Patient engagement is crucial in a chronic illness like MS which requires lifelong therapy and decision-making related to treatment, interventions, services and QoL (Heesen, et al., 2011). Patient-reported outcomes (PRO's) promote patient engagement by introducing a more holistic approach to disease management by incorporating outcomes affecting many aspects of patients' QoL (Reickmann, 2015).

Several studies have evaluated decision making in MS by assessing where MS patients seek health information, how evidence-based treatment option information is provided, patient engagement in decision making and the role of shared decision-making in MS (Hill, et al., 2012; Heesen, et al., 2004; Marrie, et al., 2013; Pietrolongo, et al., 2013). The assessment of decisional role preferences, risk knowledge and information interests in MS patients shows that decisions about treatments are very sensitive to patient choice and MS patients' active role in the decision making process is higher compared to patients with other diseases (Heesen, et al., 2004).

Shared decision-making in clinical practice has the potential to improve personal relationships between patients and healthcare providers, motivate patients to be engaged in their care, help patient choose options based on their personal values and improve adherence to treatment choices (Stacey, et al., 2008). MS is a disease of many uncertainties and shared decision-making should enhance patients' sense of control and autonomy (Heesen, et al., 2011). Lack of autonomy was identified through the concept analysis as a strong predictor of reduced QoL (Mitchell, et al., 2005). The decision-making process experienced by the patients enrolled in the MS/SCT was an example of shared decision-making. The results of the secondary analysis will not only increase the understanding of the impact of the treatment on QoL but may also help to inform patients' decisions regarding this treatment as an option.

Knowledge Translation. Despite over 28 years of research on QoL in MS, a longer history recognizing QoL as an achievement of nursing practice and the development of disease specific QoL measurement tools, the assessment of QoL from a patient perspective has not been routinely integrated into clinical practice (Solari, 2005). Several factors were identified to explain the slow translation of QoL finding into practice which include: a lack of consensus of one measurement tool; how and when to integrate the assessment of QoL into routine care; finding an appropriate setting and mode of administration; achieving buy-in of patients and healthcare team; how to collect, interpret, store and retrieve the data; allowing sufficient time for tool completion and minimizing disruption to routine practice (Reickmann, et al., 2015; Solari, 2005).

Considerable resources are dedicated to MS research and as is frequently seen in health sciences research, the translation of research findings into practice is often slow and disorganized (Graham, et al., 2006). Knowledge translation is a process of turning knowledge into action and

encompasses the processes of both knowledge creation and knowledge application (Graham, et al., 2006). The Knowledge to Action cycle is a theoretical framework that was developed to translate research findings into practice (Graham, et al., 2006). The framework was based on a review of more than 30 planned action theories and is used by the Canadian Institutes of Health Research (CIHR) as their model for knowledge translation (CIHR, 2008; Graham, et al., 2006; Straus, et al., 2013). The framework provides guidance in assessing facilitators and barriers of knowledge translation and adapting the knowledge to the needs, priorities and resources of the local context (Graham, et al., 2006; Harrison, et al., 2013). The knowledge to action process should be recommended in future QoL in MS research to ensure findings are translated in practice. Incorporating QoL measures into clinical practice will escalate once the understanding of them increases (Reickmann, et al., 2015). QoL measures have been included as an element in healthcare evaluation, health service evaluation, disease registries, epidemiological studies, drug research and development, and clinical trials so the time has come to implement them into clinical practice (Reickmann, et al., 2015; Riazi, 2006). Two knowledge translation issues are identified as a result of this thesis; 1) knowledge translation of research findings and 2) integration of QoL assessment into practice. The knowledge translation plan for the findings of this thesis is to publish both the findings from the concept analysis and the results of the secondary analysis as well as present the findings at the annual meeting of the Consortium of MS Centres. The second issue will be a future implication for my nursing practice.

Implications for Nursing

The results of the concept analysis and the proposed QoL study in this thesis have implications for nursing at various levels in outpatient clinic care, inpatient hospital care, and community care. The implications for advanced practice nurses (APN) will be highlighted as

their role is expanding in MS care (Morgante, et al., 2006; Halper, 2007). An APN is a nurse practicing at an advanced level of clinical practice who maximizes the use of graduate education, specialized nursing knowledge and expertise to meet the health needs of individuals, families, groups, communities and populations (Canadian Nurses Association, 2008). The APN role entails five core competencies of direct clinical practice, education, consultation, leadership, and research. Nursing implications for QoL in MS are acknowledged for each APN competency (Table 4.1).

Table 4.1: Implications of Concept Analysis and Secondary Analysis Proposal for APN

APN Competency	Implications of thesis findings for APN
1. Direct Clinical Practice	<ul style="list-style-type: none"> • Demonstrate advanced knowledge of MS patient care needs affecting QoL • Assess complex practice issues for MS patients with aggressive disease or demonstrating diminished QoL <p>Future Implications:</p> <ul style="list-style-type: none"> • Engage MS patients and families in discussion about factors influencing QoL • Assess the facilitators and barriers to implement assessment of QoL in MS care environment • Participate in shared decision-making with patients to choose evidence-based treatment options that reflect their own values and QoL
2. Education	<ul style="list-style-type: none"> • Participate in institutional and community educational programs for MS consumers and health professionals <p>Future Implications</p> <ul style="list-style-type: none"> • Educate patients, families and healthcare providers on the benefits of including patient’s perspective of QoL • Provide training related to assessing and interpreting QoL in MS • Apply relevant research and theories of QoL in MS to clinical practice using critical thinking and decision-making
3. Collaboration/ Consultation	<ul style="list-style-type: none"> • Facilitate a collaborative, interdisciplinary team practice model in the care of MS patients to support QoL needs • Liaise with community care partners (MS Society, Community Care Access Centre) <p>Future Implications</p> <ul style="list-style-type: none"> • Provide consultation to nursing staff, managers, coordinators, physicians and other team members regarding clinical and professional practice issues related to QoL in MS and treatment for aggressive disease

<p>4. Research</p>	<ul style="list-style-type: none"> • Prepare abstracts and present QoL findings both locally and at international conferences • Collect, prepare and analyse QoL data <p>Future Implications</p> <ul style="list-style-type: none"> • Plan for knowledge translation through publication and presentation of concept analysis findings and results of QoL data from MS/BMT study • Utilize the Knowledge to Action cycle to implement the use of a QoL assessment tool into clinical practice • Assess the possibility of implementing a QoL tool in conjunction with shared decision making • Collaborate with interdisciplinary research teams to implement PRO's into new MS research studies • Advocate for consistent QoL measures
<p>5. Leadership</p>	<ul style="list-style-type: none"> • Provide leadership in development, implementation and evaluation of research initiatives related to MS <p>Future Implications</p> <ul style="list-style-type: none"> • Mentor MS nursing colleagues and others to improve and support nursing practice for MS patients related to QoL • Collaborate with academic institutions through shared projects and/or through joint appointments

Conclusion

This thesis has explored QoL as it relates to individuals living with MS. The concept analysis (Chapter 3) provided a review of the MS research with an evolutionary, sociocultural and multidisciplinary perspective and the results show the far reaching impact of QoL for patients, families, healthcare providers and researchers. The proposal for the secondary analysis (Chapter 4) study evaluating QoL data collected on patients with aggressive MS undergoing an aggressive treatment will provide insight into the impact of a novel treatment for MS on QoL. The translation of the results will contribute to the requirement of escalated understanding of QoL in MS and provide the opportunity to implement the assessment of QoL in the routine practice of MS care.

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Chapter Five

Co-Authorship Contributions and Acknowledgments

Contributions of Collaborators

Co-Authorship

Several authors contributed to this thesis. Marjorie Bowman RN, BScN (MB) conceived, participated in, and directed all aspects of this research project in partial fulfillment of the requirements for a Master's Degree in Nursing at the University of Ottawa. MB is an Advanced Practice Nurse at The Ottawa Hospital specializing in multiple sclerosis and neurology. She was the research coordinator for the MS/SCT Study. She is a member of RNAO, Canadian Associations of Neuroscience Nurses (CANN), and The International Organization of MS Nurses (IOMSN).

Four thesis committee members, Dr. Janet Squires RN, PhD (JS) (supervisor), Dr. Dawn Stacey RN, PhD, CON(C) (DS), Dr. Lisa Walker PhD, C.Psych (LW), and Dr. Harold Atkins MD, FRCPC (HA) also participated in different phases of the thesis. JS and DS participated in study design, development of thesis proposal, analysis and interpretation of data, edits and revisions as well as final approval of the thesis for evaluation. LW and HA participated in study design, analysis of data, edits and revisions.

JS is assistant professor in the School of Nursing at the University of Ottawa and is a scientist in the Clinical Epidemiology Program, Ottawa Hospital Research Institute. She holds a University Research Chair in Health Evidence Implementation (2015-2020) and CIHR New Investigator (2014-2019). Her research interests include knowledge translation; organizational context; measurement (survey development and psychometric evaluation); and quantitative, mixed methods and systematic review research.

DS is a full professor in the School of Nursing at the University of Ottawa and is a scientist at the Ottawa Hospital Research Institute where she is Director of the Patient Decision

Aids Research Group. She holds a Research Chair in Knowledge Translation to Patients. Her research interests include: knowledge translation to patients; patient decision aid development, evaluation and appraisal; decision coaching; implementation of decision aids and decision coaching into practice; telephone-based care, and interprofessional approaches to shared decision making.

LS is a neuropsychologist at The Ottawa Hospital and a clinician investigator in the Neuroscience Program at Ottawa Hospital Research Institute. She is an adjunct professor in the Faculty of Medicine, a clinical professor in the School of Psychology and in the Faculty of Graduate and Postdoctoral Studies at University of Ottawa. She is also an adjunct research professor, Department of Psychology and Institute of Cognitive Science at Carleton University. Her research interests include cognition in multiple sclerosis in the areas of longitudinal evaluation of cognition, information processing speed, cognitive fatigue, the interaction between cognition and mood, the relationship between cognition and both structural and functional neuroimaging variables, cognitive effects of immunoablative hematopoietic stem cell transplant in MS, cognitive effects of mesenchymal stem cell therapy, methods of screening for cognitive impairment when comprehensive neuropsychological evaluation is not possible and mindfulness and its relationship to cognition and wellness variables in MS.

HA is a scientist in the Cancer Therapeutics Program at the Ottawa Hospital Research Institute, Associate Professor in Clinical Hematology at University of Ottawa and attending physician, Blood and Marrow Transplant Program at The Ottawa Hospital. His research interests include stem cell transplant for autoimmune diseases and oncolytic virus research for the treatment of human marrow derived malignancies.

Appendices

Appendix A

Conceptual Framework for Health-Related Quality of Life Definitions

Characteristics of the individual: demographic, developmental, psychological and biological factors that influence health outcomes

Characteristics of the environment: Social factors include influence of family, friends and healthcare providers. Physical factors include settings such as home, neighbourhood and workplace that influence health outcomes either positively or negatively.

Biological functions: The dynamic processes that support life (molecular, cellular and whole organ level).

Symptoms: A patient's perception of an abnormal physical, emotional or cognitive state.

Functional status: Focus on optimization of function that remains in 4 dimensions (functional capacity, functional performance, functional capacity utilization and functional reserve).

General health perceptions: Subjective component commonly measured with a single global question to ask people to rate their health on a Likert scale ranging from poor to excellent.

Overall quality of life: Subjective well-being related to how happy or satisfied a person is with life as a whole within the domains of health and functioning, psychological and spiritual, family, social and economic.

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Appendix B

Multiple Sclerosis Quality of Life
(MSQOL)-54 Instrument

For Further Information, Contact:

Barbara G. Vickrey, MD, MPH
UCLA Department of Neurology
C-128 RNRC; Box 951769
Los Angeles, CA 90095-1769
Voice: 310.206.7671
Fax: 310.794.7716

INSTRUCTIONS:

This survey asks about your health and daily activities. Answer every question by circling the appropriate number (1, 2, 3, ...).

If you are unsure about how to answer a question, please give the best answer you can and write a comment or explanation in the margin.

Please feel free to ask someone to assist you if you need help reading or marking the form.

1. In general, would you say your health is:
(circle one number)

- 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 number)

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

3-12. The following questions are about activities you might do during a typical day. Does **your health** limit you in these activities? If so, how much?
 (Circle 1, 2, or 3 on each line)

	Yes, Limited a Lot	Yes, Limited a Little	No, Not Limited at All
3. Vigorous activities , such as running, lifting heavy objects, participating in strenuous sports	1	2	3
4. Moderate activities , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
5. Lifting or carrying groceries	1	2	3
6. Climbing <u>several</u> flights of stairs	1	2	3
7. Climbing <u>one</u> flight of stairs	1	2	3
8. Bending, kneeling, or stooping	1	2	3
9. Walking <u>more than a mile</u>	1	2	3
10. Walking <u>several blocks</u>	1	2	3
11. Walking <u>one block</u>	1	2	3
12. Bathing and dressing yourself	1	2	3

13-16. 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
13. Cut down on the amount of time you could spend on work or other activities	1	2
14. Accomplished less than you would like	1	2
15. Were limited in the kind of work or other activities	1	2
16. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

17-19. 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
17. Cut down on the amount of time you could spend on work or other activities	1	2
18. Accomplished less than you would like	1	2
19. Didn't do work or other activities as carefully as usual	1	2

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

(circle one number)

- Not at all..... 1
- Slightly2
- Moderately3
- Quite a bit4
- Extremely.....5

Pain

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

(circle one number)

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

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

(circle one number)

- Not at all..... 1
- A little bit 2
- Moderately 3
- Quite a bit 4
- Extremely..... 5

23-32. 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...** (Circle one number on each line)

	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
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6
32. Did you feel rested on waking in the morning?	1	2	3	4	5	6

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

(circle one number)

All of the time.....1

Most of the time.....2

Some of the time3

A little of the time.....4

None of the time.....5

Health in General

- 34-37. How TRUE or FALSE is each of the following statements for you.

(Circle one number on each line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
34. I seem to get sick a little easier than other people	1	2	3	4	5
35. I am as healthy as anybody I know	1	2	3	4	5
36. I expect my health to get worse	1	2	3	4	5
37. My health is excellent	1	2	3	4	5

Health Distress

How much of the time during the **past 4 weeks...**

(Circle one number on each line)

	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
38. Were you discouraged by your health problems?	1	2	3	4	5	6
39. Were you frustrated about your health?	1	2	3	4	5	6
40. Was your health a worry in your life?	1	2	3	4	5	6
41. Did you feel weighed down by your health problems?	1	2	3	4	5	6

Cognitive Function

How much of the time during the **past 4 weeks...**

(Circle one number on each line)

	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
42. Have you had difficulty concentrating and thinking?	1	2	3	4	5	6
43. Did you have trouble keeping your attention on an activity for long?	1	2	3	4	5	6
44. Have you had trouble with your memory?	1	2	3	4	5	6
45. Have others, such as family members or friends, noticed that you have trouble with your memory or problems with your concentration?	1	2	3	4	5	6

Sexual Function

46-50. The next set of questions are about your sexual function and your satisfaction with your sexual function. Please answer as accurately as possible about your function **during the last 4 weeks only.**

How much of a problem was each of the following for you **during the past 4 weeks?**

(Circle one number on each line)

MEN	Not a problem	A Little of a Problem	Somewhat of a Problem	Very Much a Problem
46. Lack of sexual interest	1	2	3	4
47. Difficulty getting or keeping an erection	1	2	3	4
48. Difficulty having orgasm	1	2	3	4
49. Ability to satisfy sexual partner	1	2	3	4

(Circle one number on each line)

WOMEN	Not a problem	A Little of a Problem	Somewhat of a Problem	Very Much a Problem
46. Lack of sexual interest	1	2	3	4
47. Inadequate lubrication	1	2	3	4
48. Difficulty having orgasm	1	2	3	4
49. Ability to satisfy sexual partner	1	2	3	4

50. Overall, how satisfied were you with your sexual function **during the past 4 weeks?**

(circle one number)

- Very satisfied..... 1
- Somewhat satisfied 2
- Neither satisfied nor
dissatisfied 3
- Somewhat dissatisfied 4
- Very dissatisfied 5

51. During the **past 4 weeks**, to what extent have problems with your bowel or bladder function interfered with your normal social activities with family, friends, neighbors, or groups?

(circle one number)

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

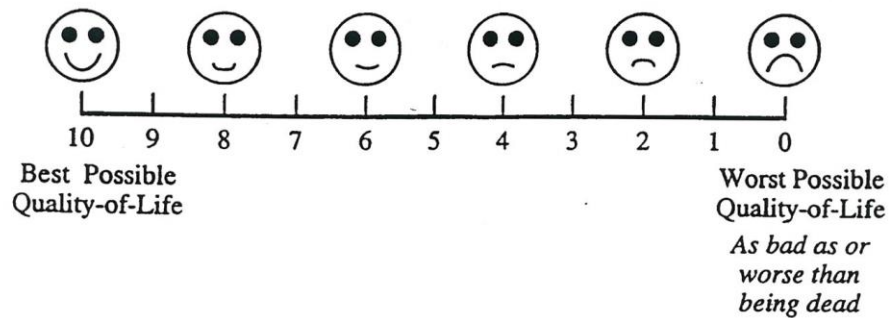
52. During the **past 4 weeks**, how much did *pain* interfere with your enjoyment of life?

(circle one number)

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

53. Overall, how would you rate your own quality-of-life?

Circle one number on the scale below:



54. Which best describes how you feel about your life as a whole?

(circle one number)

- Terrible 1
- Unhappy 2
- Mostly dissatisfied 3
- Mixed - about equally
satisfied and dissatisfied 4
- Mostly satisfied 5
- Pleased 6
- Delighted 7

Appendix C

Scoring Forms for Multiple Sclerosis Quality of Life (MSQOL) -54

Table 1
MSQOL-54 Scoring Form

Table 2
MSQOL-54 Physical Health Composite Score

Table 3
MSQOL-54 Mental Health Composite Score

MSQOL-54 Scoring Form

Table 1

Scale/Item Number	Response						Subtotal	Final Score 0-100 point scale
	1	2	3	4	5	6		
Physical Health								
3.	0	50	100				_____	
4.	0	50	100				_____	
5.	0	50	100				_____	
6.	0	50	100				_____	
7.	0	50	100				_____	
8.	0	50	100				_____	
9.	0	50	100				_____	
10.	0	50	100				_____	
11.	0	50	100				_____	
12.	0	50	100				_____	
							Total: _____ + 10 = _____	
Role limitations due to physical problems								
13.	0	100					_____	
14.	0	100					_____	
15.	0	100					_____	
16.	0	100					_____	
							Total: _____ + 4 = _____	
Role limitations due to emotional problems								
17.	0	100					_____	
18.	0	100					_____	
19.	0	100					_____	
							Total: _____ + 3 = _____	
Pain								
21.	100	80	60	40	20	0	_____	
22.	100	75	50	25	0		_____	
52.	100	75	50	25	0		_____	
							Total: _____ + 3 = _____	
Emotional well-being								
24.	0	20	40	60	80	100	_____	
25.	0	20	40	60	80	100	_____	
26.	100	80	60	40	20	0	_____	
28.	0	20	40	60	80	100	_____	
30.	100	80	60	40	20	0	_____	
							Total: _____ + 5 = _____	
Energy								
23.	100	80	60	40	20	0	_____	
27.	100	80	60	40	20	0	_____	
29.	0	20	40	60	80	100	_____	
31.	0	20	40	60	80	100	_____	
32.	100	80	60	40	20	0	_____	
							Total: _____ + 5 = _____	
Table 1 (cont.)								
Scale/Item Number	Response						Subtotal	Final Score 0-100 point
	1	2	3	4	5	6		

Health Perceptions									
1.	100	75	50	25	0		_____		
34.	0	25	50	75	100		_____		
35.	100	75	50	25	0		_____		
36.	0	25	50	75	100		_____		
37.	100	75	50	25	0		_____		
	Total:						_____ + 5 = _____		
Social function									
20.	100	75	50	25	0		_____		
33.	0	25	50	75	100		_____		
51.	100	75	50	25	0		_____		
	Total:						_____ + 3 = _____		
Cognitive function									
42.	0	20	40	60	80	100	_____		
43.	0	20	40	60	80	100	_____		
44.	0	20	40	60	80	100	_____		
45.	0	20	40	60	80	100	_____		
	Total:						_____ + 4 = _____		
Health distress									
38.	0	20	40	60	80	100	_____		
39.	0	20	40	60	80	100	_____		
40.	0	20	40	60	80	100	_____		
41.	0	20	40	60	80	100	_____		
	Total:						_____ + 4 = _____		
Sexual function*									
46.	100	66.7	33.3	0			_____		
47.	100	66.7	33.3	0			_____		
48.	100	66.7	33.3	0			_____		
49.	100	66.7	33.3	0			_____		
	Total:						_____ + 4 = _____		
Change in health									
2.	100	75	50	25	0		_____		
Satisfaction with sexual function									
50.	100	75	50	25	0		_____		
Overall quality of life									
		Response							
		1	2	3	4	5	6	7	
53.		(multiply response by 10)							_____
54.	0	16.7	33.3	50	66.7	83.3	100		
	Total:						_____ + 2 = _____		

Note: The total number of items in each scale is listed as the divisor for each subtotal. However, due to missing data, the divisor might actually be less than that if not every item within a given scale has been answered. For example, if item 38 in the Health Distress scale was left blank and the other 3 items in the scale were answered, then the "Total" score for Health Distress would be divided by '3' (instead of '4') to obtain the "Final Score."

* Males and females can be combined in the analysis even though question 47 is different for the two groups. The scale scores can also be reported separately for males and females.

Table 2
Formula for calculating MSQOL-54 Physical Health Composite Score

MSQOL-54 Scale	Final Scale Score	x	Weight	=	Subtotal
Physical function	_____	x	.17	=	_____(a)
Health perceptions	_____	x	.17	=	_____(b)
Energy/fatigue	_____	x	.12	=	_____(c)
Role limitations - physical	_____	x	.12	=	_____(d)
Pain	_____	x	.11	=	_____(e)
Sexual function	_____	x	.08	=	_____(f)
Social function	_____	x	.12	=	_____(g)
Health distress	_____	x	.11	=	_____(h)
PHYSICAL HEALTH COMPOSITE: Sum subtotals (a) through (h) =					_____

Table 3
Formula for calculating MSQOL-54 Mental Health Composite Score

MSQOL-54 Scale	Final Scale Score	x	Weight	=	Subtotal
Health distress	_____	x	.14	=	_____(a)
Overall quality of life	_____	x	.18	=	_____(b)
Emotional well-being	_____	x	.29	=	_____(c)
Role limitations - emotional	_____	x	.24	=	_____(d)
Cognitive function	_____	x	.15	=	_____(e)
MENTAL HEALTH COMPOSITE: Sum subtotals (a) through (e) =					_____

Appendix D



Ottawa Health Science Network Research Ethics Board/ Conseil d'éthique de la recherche du Réseau de science de la santé d'Ottawa

Civic Box 411 725 Parkdale Avenue, Ottawa, Ontario K1Y 4E9 613-798-5555 ext. 14902 Fax . 613-761-4311
<http://www.ohri.ca/ohsn-reb>

25 September, 2015

Dr. Harold Atkins
Ottawa Hospital - General Campus
Centre for Innovative Cancer Research (OHRI)
501 Smyth Road, Box 926
Ottawa, ON
K1H 8L6

Dear Dr. Atkins:

RE: Protocol# - 2000374-01H Target Multiple Sclerosis as an Autoimmune Disease with Intensive Immunoblastic Therapy and Immunological Reconstitution - A Potential Curative Therapy for Patients with Predicted Poor Prognosis MS

Renewal Expiry Date - 24 September, 2016

Thank you for the email of September 22, 2015 from Marjorie Bowman. It was noted that ethical approval lapsed from August 28, 2015 to September 24, 2015 but that no data was collected. I am pleased to inform you that your Annual Renewal Request was reviewed by the Ottawa Health Science Network Research Ethics Board (OHSN-REB) and is approved. No changes, amendments or addenda may be made in the protocol or the consent form without the OHSN-REB's review and approval.

Renewal is valid for a period of one year. Approximately one month prior to that time, a single renewal form should be sent to the REB office.

The extended study end date to June 30, 2016 has been approved.

OHSN-REB complies with the membership requirements and operates in compliance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; the International Conference on Harmonization - Good Clinical Practice: Consolidated Guideline; and the provisions of the Personal Health Information Protection Act 2004.

Chairperson
Ottawa Health Science Network Research Ethics Board

/km



Ottawa Health Science Network Research Ethics Board/ Conseil d'éthique de la recherche du Réseau de science de la santé d'Ottawa

Civic Box 411 725 Parkdale Avenue, Ottawa, Ontario K1Y 4E9 613-798-5555 ext. 14902 Fax : 613-761-4311
<http://www.ohri.ca/ohsn-reb>

Monday, November 24, 2014

Dr. Harold Atkins
 Ottawa Hospital - General Campus
 Centre for Innovative Cancer Research (OHRI)
 501 Smyth Road, Box 926
 Ottawa, ON
 K1H 8L6

Dear Dr. Atkins:

Re: Protocol # 2000374-01H Target Multiple Sclerosis as an Autoimmune Disease with Intensive Immunoblastic Therapy and Immunological Reconstitution - A Potential Curative Therapy for Patients with Predicted Poor Prognosis MS

Thank you for the letter from Ms. M. Bowman dated November 18, 2014, with the signed additional co-investigator, adding Marjorie Bowman as a co-investigator, and the revised page 1 of the Protocol, adding version 4 dated November 2, 2014.

PLEASE NOTE: THE APPROVAL OF THIS sub-study with Ms. Marjorie Bowman IS CONDITIONAL UPON A FULLY-SIGNED STUDY CONTRACT/AGREEMENT BETWEEN THE OTTAWA HOSPITAL RESEARCH INSTITUTE, THE PRINCIPAL INVESTIGATOR AND THE SPONSOR (OR AS OTHERWISE REQUIRED). YOU CANNOT START THE STUDY, OR BEGIN TO RECRUIT RESEARCH PARTICIPANTS INTO THE STUDY UNTIL THE STUDY CONTRACT/AGREEMENT HAS BEEN SIGNED BY ALL PARTIES, AND HAS BEEN RECEIVED BY THE OTTAWA HOSPITAL RESEARCH INSTITUTE'S CONTRACTS OFFICE. FOR FURTHER DETAILS, PLEASE CONTACT CHRISTINE LAFONTAINE, CONTRACTS ADMINISTRATOR AT CHRILAFONTAINE@OHRI.CA OR AT 613-798-5555 EXT. 19690.

Therefore, the following documents have been given conditional approval:

- OHSN-REB protocol amendment report dated October 14, 2014
- Master of Science in Nursing: Research Proposal, version 4, dated November 2, 2014

Ms. Marjorie Bowman has now been added as a co-investigator. She has removed as a staff member.

Study approval remains in effect until August 27, 2015.

OHSN-REB complies with the membership requirements and operates in compliance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; the International

.../2

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Conference on Harmonization - Good Clinical Practice: Consolidated Guideline; and the provisions of the Personal Health Information Protection Act 2004.

Yours sincerely,

A rectangular area containing a dense, black scribbled-out signature, completely obscuring the name of the signatory.

Chairman
Ottawa Health Science Network Research Ethics Board

/cb

**Data Sharing Agreement ("Agreement")
Research Use of Data**

BETWEEN:	AND
Ottawa Hospital Research Institute 725 Parkdale Avenue, Ottawa, Ontario K1Y 4E9	University of Ottawa 75 Laurier Avenue East Ottawa, Ontario K1N 6N5
Ottawa Hospital Research Institute Principal Investigator: Dr. Harold Atkins (together with Ottawa Hospital Research Institute = "OHRI")	University of Ottawa Investigator: Dr. Janet Squires (together with University of Ottawa = "UOttawa")
Name of Study ("Study"): Targeting Multiple Sclerosis as an Autoimmune Disease with Intensive Immunoblastic Therapy and Immunological Reconstitution - A Potential Curative Therapy for Patients with Predicted Poor Prognosis MS	
OHRI REB Study Number: 2009374-01H	UOTTAWA Study Number: A01-16-01

De-identified data to be provided ("Data"): As per the REB approved Study Protocol, incorporated herein by reference.

This Agreement, effective as of the last date of signature below, is entered into between the parties to govern the transfer of Data between OHRI and UOttawa to be used for the purposes of a secondary analysis of the quality of life (MSQoL-54) data collected in this Study as part of Marjorie Bowman's Masters' of Science Thesis at UOttawa and in accordance with this Agreement. The party providing the Data is the "PROVIDER" and the party receiving the Data is the "RECIPIENT."

PROVIDER will prepare and furnish to RECIPIENT the Data in accordance with applicable laws, and specifically warrants that transfer of the Data by PROVIDER will be in compliance with REB approved subject informed consent forms ("ICFs") provided by the individuals from whom the Data were collected, or terms of an REB Waiver of Consent, as applicable. Data will not be transferred until each party's REB provides written approval for the Study.





RECIPIENT shall use the Data in compliance with all applicable laws; and shall specifically only use or disclose the Data for the conduct of the Study in accordance with the permitted uses of the Data specified in the applicable ICFs or REB Waiver of Consent, or otherwise as required by law. No right, title or interest in and to the Data is granted or implied to the RECIPIENT hereunder.

RECIPIENT shall have the right to use (1) the analyzed, de-identified data it derives from the use of the Data, and (2) de-identified information and results arising out of its analysis of the Data, as part of a publication or presentation of the results of the Study, and shall own such de-identified, analyzed data and results. RECIPIENT shall not include any personally identifying information in any publication or presentation. PROVIDER's contribution to the Study shall be acknowledged appropriately in any such publication or presentation in accordance with academic standards.

RECIPIENT shall use appropriate safeguards to prevent any unauthorized use or disclosure of the Data and shall report to the PROVIDER any unauthorized use or disclosure of which RECIPIENT becomes aware, or of any breach of this Agreement. RECIPIENT shall not use the Data to identify or contact the individuals from whom such Data was collected. RECIPIENT shall securely destroy the Data as required by the Protocol or PROVIDER and provide a written confirmation of the manner of destruction in a form acceptable to PROVIDER. PROVIDER may conduct audits of the RECIPIENT concerning the maintenance of appropriate security safeguards to ensure compliance with this Agreement.

RECIPIENT shall give access to the Data only to its staff with a need to know for the purpose of conducting the Study, and who are bound by RECIPIENT to comply with the terms of this Agreement.

This Agreement may be signed in counterparts, and each counterpart may be delivered by facsimile or signed PDF by email. Each counterpart shall constitute an original, and when taken together, shall constitute one and the same instrument.

Ottawa Hospital Research Institute  Director, Research Administration	University of Ottawa  UOTTAWA
OHRH INVESTIGATOR 	and UOTTAWA INVESTIGATOR 

Read and Acknowledged By:

 2015
Date

Appendix E



Université d'Ottawa University of Ottawa

Bureau d'éthique et d'intégrité de la recherche Office of Research Ethics and Integrity

February 10th, 2015

Marjorie Bowman
MA Student
School of Nursing
Faculty of Health Sciences
University of Ottawa
mbowman@toh.on.ca

Janet Squires
Supervisor
School of Nursing
Faculty of Health Sciences
University of Ottawa
jasquires@toh.on.ca

Re: U of O Ethics file no. A01-15-01 – “Target Multiple Sclerosis as an Autoimmune Disease with Intensive Immunoblastic Therapy and Immunological Reconstitution - A Potential Curative Therapy for Patients with Predicted Poor Prognosis MS”

Dear Ms. Bowman and Dr. Squires,

Thank you for the protocol documents and Certificate of Approval from the OHSN-REB (#2000374-01H) for your project named above.

This is to confirm that, in accordance with the agreement between the University of Ottawa and the OHSN-REB, the University of Ottawa has authorized this board to act as Board of Record for the review and oversight of research involving human subjects conducted at or through the hospital.

We remind you of your obligation to:

- Follow all procedures of the OHSN-REB including reporting and renewal procedures;
- Submit to the authority of the OHSN-REB and that you are subject to OHSN-REB requirements, including, without limitation, the requirement to modify or stop the research on demand of the OHSN-REB.

If you have any questions, please contact our ethics office at 562-5387.

Sincerely yours,

Director
Office of Research Ethics and Integrity

550, rue Cumberland Ottawa (Ontario) K1N 6N5 Canada 550 Cumberland Street
Ottawa, Ontario K1N 6N5 Canada

(613) 562-5387 • T2lec. Fax (613) 562-5338
<http://www.rech.rihe.uottawa.ca/ideontologie/>
<http://www.research.uottawa.ca/ethics/>