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A Comparison of Quality of Life between Intense and Non-Intense Treatment for Patients with Acute Myeloid Leukemia and High-Risk Myelodysplastic Syndrome

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A Comparison of Quality of Life between Intense and Non-Intense Treatment for
Patients with Acute Myeloid Leukemia and High-Risk Myelodysplastic Syndrome

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree
Doctor of Philosophy
College of Nursing
University of South Florida

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DEDICATION

I dedicate this dissertation to my husband, Joseph Vance, who pushed me through the difficult times and was a constant source of support and encouragement. I also dedicate this work to my parents, Jack and Jean Bentley, without whom this would have been impossible. Finally, I thank my sons, Robert “Robby” Tinsley and Benjamin “BJ” Tinsley who made tables and formatting less formidable.

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TABLE OF CONTENTS

List of Tables	iii
List of Figures	iv
Abstract	v
Chapter One: Introduction	1
Treatment	2
Quality of Life	5
Statement of the Problem	5
Statement of the Purpose	6
Specific Aims	6
Definition of Relevant Terms	7
Assumptions	8
Significance of the Study	8
Chapter Two: Review of Literature	9
Theoretical Background	9
Age for High Risk MDS and AML Patients	10
Fatigue for High Risk MDS and AML Patients	11
Comorbidities and QOL	12
QOL in Myelodysplastic Syndromes	14
QOL in AML	17
Conclusions	21
Chapter Three: Methods	23
Study Design	23
Setting	23
Sample	23
Measures	24
FACT-Leukemia	25
Brief Fatigue Inventory	25
Charlson Comorbidity Index	25
Demographic Data	26
Procedures	26
Data Analysis	27
Aim One: QOL from Week 1 to Week 4	27
Aim Two: Predictors of QOL	27
Aim Three: Moderators of QOL	27

Chapter Four: Results	28
Sample	28
Descriptive Data	31
Aim One: QOL from Week 1 to Week 4	31
Aim Two: Predictors of QOL	32
Aim Three: Moderators of QOL	33
Chapter Five: Discussion, Implications, and Conclusions	36
Sample	36
Descriptive Data	37
Aim One: QOL from Week 1 to Week 4	38
Aim Two: Predictors of QOL	40
Aim Three: Moderators of QOL	40
Implications for Nursing	42
Implications for Future Research	43
Study Limitations	43
Conclusions	44
References	45
Appendices	56
Appendix A: Institutional Review Board Approval	57
Appendix B: Scientific Review Committee Approval	59
Appendix C: Charlson Comorbidity Index	60
Appendix D: Terms and Conditions for Use of Charlson Comorbidity Index	63
Appendix E: Demographic Questionnaire	64
Appendix E: Brief Fatigue Inventory	65
Appendix G: Authorization to Use Brief Fatigue Inventory	66
Appendix H: FACT Leukemia Questionnaire	67
Appendix I: FACT-Leu Licensing Agreement	70
Appendix J: Informed Consent	71

LIST OF TABLES

Table 1: Frequencies and Percentages of Demographic Variables	29
Table 2: Mean, Range, and Standard Deviation of Age for Groups	29
Table 3: Chi Square and Paired t-Test for Demographic Variables between Intense and Non-intense Treatment for Subjects who Completed both QOL Measures	30
Table 4: Frequencies of Diagnoses	30
Table 5: Means and Standard Deviations of Instruments	31
Table 6: Repeated Measures Analysis of Variance of Group, Time, and Group by Time (N=67) for QOL Scores	31
Table 7: Repeated Measures Analysis of Variance for Time by Groups	32
Table 8: Correlation of Predictors with QOL from FACT-Leu 1 (N=85)	32
Table 9: Correlation of Diagnosis with QOL from FACT-Leu 1 (N=85)	32
Table 10: Regression of Predictor Variables on QOL on FACT-Leu 2	33
Table 11: Linear Regression FACT-Leu 2 from Moderator, Type of Treatment, and Age	33
Table 12: Coefficients for Type of Treatment, Age, and Moderator Effects on QOL	34
Table 13: Regression of FACT-Leu 2 from Moderator, Type of Treatment, and Fatigue	35
Table 14: Coefficients for Type of Treatment, Fatigue, and Moderator	35

LIST OF FIGURES

Figure 1: Conceptual Model for the Study

22

ABSTRACT

Acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS) are hematologic malignancies that occur most frequently in the sixth and seventh decades of life. Both disorders are associated with a poor prognosis, with median survival of one year or less. An overall five-year survival rate for both disorders, regardless of treatment, is less than 10%. A primary goal of treatment is to improve quality of life (QOL) because cure is improbable. The purpose of this longitudinal cohort study was to compare QOL between groups, intensive, non-intensive therapy, and supportive care. The sample consisted of 85 patients with high risk MDS and AML recruited from Moffitt Cancer Center. Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) was used to measure QOL. The aims for the study were to: 1) To compare the difference in QOL scores measured by the Functional Assessment of Cancer Therapy –Leukemia version for intensive chemotherapy, non-intensive therapy and supportive care within 7 days of new treatment and one month after initiation of treatment; 2) To determine QOL predictors of AML and high risk MDS from age, comorbidity, fatigue, and diagnosis; 3) To test the moderating effect of treatment with age, comorbidity, and fatigue on QOL.

The first aim was analyzed with repeated measures analysis of variance (ANOVA). The supportive care group was not included in the analysis because of low accrual. Results indicated that there was a significant group by time interaction (with $p=.040$). Follow up tests revealed that the intensive treatment group had a significant improvement in their QOL scores at 1 month post treatment ($p=.020$). The second aim was conducted using Pearson's correlations with age, comorbidity, fatigue, and diagnosis with significant correlations found between fatigue and QOL

($r=-.693$, $p<.001$). These findings identify an important relationship between fatigue and QOL. This was a negative correlation, showing that as fatigue increases QOL decreases. The third aim was explored using regression with Hayes (2013) application for moderation analysis. Scores for QOL for age, comorbidity, and fatigue were not moderated by treatment.

These findings suggest that the most intensive treatment approach improves QOL. In addition, fatigue is a significant predictor of QOL. As fatigue increases, QOL scores decrease. Additional studies with a larger, more diverse sample is needed to explore the relationship between treatment approaches and QOL. In addition, intervention studies can be developed in AML and high risk MDS focused on fatigue management. It is anticipated that the results of this study will be used to inform patients and health care providers when making decisions concerning treatment based on QOL outcomes.

CHAPTER ONE:

INTRODUCTION

Patients with acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS) face the difficult decision of choosing the best treatment approach, knowing that their prognosis is poor. Unfortunately, few studies are available to help health care providers guide patients in choosing treatments based on quality of life (QOL).

Both AML and MDS are bone marrow malignancies that occur commonly in older patients, in whom optimal treatment remains controversial (Klepin, Rao, & Pardee, 2014). Treatment can range from supportive care to hematopoietic stem cell transplant. The diseases are often studied together because they have similar disease characteristics, life expectancy (for high-risk disease), age, comorbidities, and treatment options (Klepin et al., 2014; Merkel et al., 2013; Sekeres et al., 2004). The most common form of adult acute leukemia is AML with approximately 18,860 cases diagnosed and 10,460 deaths in 2014 (American Cancer Society, 2014). The median age of diagnosis in the United States is 67 years, according to the National Cancer Institute Surveillance Epidemiology and End Results data (SEER, 2015). MDS incidence using a claims-based algorithm in conjunction with SEER data project approximately 50,000 cases per year in the United States, with a median age of 76 years (Craig, Rollison, List, & Cogle, 2012). Approximately 20,000 cases of MDS are high risk (Ma, Does, Raza, & Mayne, 2007).

High risk MDS is determined by calculating an individual score, the International Prognostic System Score, from unique patient characteristics including number of cytopenias,

percentage of marrow blasts, and cytogenetic abnormalities (Greenberg et al., 1997).

Determination of treatment is based on age, performance status, comorbidities, and patient preference (NCCN, 2015). High risk MDS and AML are treated in the same way, have a similar prognosis, and are grouped for comparison in this study.

Treatment

Standard treatment for AML patients 60 years of age and older is based on performance status, prior hematologic disorder, presence of unfavorable cytogenetic or molecular abnormalities, and whether it is related to prior chemotherapy or radiation therapy (NCCN, 2015). Treatment recommendations for patients with an Eastern Cooperative Oncology Group performance status of 0-2 include clinical trial, intense chemotherapy with induction chemotherapy, and non-intensive chemotherapy with azacitidine or decitabine. Clinical trial, non-intensive chemotherapy, and best supportive care are recommended for patients who have a performance status greater than two, or significant comorbidities, or are older than 75. Intense chemotherapy includes treatment with cytosine arabinoside and an anthracycline administered in the hospital, with an anticipated length of hospitalization of four to six weeks, and a cure rate of 35% (Estey, 2006). The majority of AML and high-risk MDS patients are not able to tolerate hematopoietic stem cell transplant, which is the standard of care for many younger patients (Baron & Storb, 2007). According to SEER data (2015), the five-year relative survival rate from 2007 to 2012 was 25.9% for adults. In contrast, the five-year disease free survival rates for AML patients 65 years of age and older was only 5%. Survival rates for older AML patients have not changed in the past three decades (Erba, 2007). Studies are ongoing to try to improve the overall survival and cure for this distinct population of patients (Burnett et al., 2010; Burnett, Wetzler, &

Lowenberg, 2011). In contrast, few studies have focused on the quality of their survival with different treatment approaches (Leach et al., 2006).

The goal of treatment with high risk MDS is to maintain the best QOL and improve survival. Cure is impossible without an allogeneic stem cell transplant. The National Comprehensive Cancer Network (NCCN) recommends that age, performance status, and comorbidities determine appropriate therapy (2015). Patients should receive supportive care, which includes evaluation of QOL, psychosocial support, transfusions with blood products when needed, and infection management (NCCN, 2015). Treatment recommendations for high risk MDS include low intensity therapy with a hypomethylating agent such as azacitidine or decitabine. Hypomethylating agents are administered in the outpatient setting monthly, for as long as the patient responds, or development of adverse side effects. Allogeneic stem cell transplant is considered if the patient is healthy, and has a human leukocyte antigen identical donor (NCCN, 2015; Giralt, Horowitz, Weisdorf, & Cutler 2011).

The majority of AML and high risk MDS patients die within five years with or without standard treatment (Garcia-Manero, & Fenaux, 2011; Estey, 2007). To prevent unnecessary suffering, it is important to understand how the treatment influences QOL for these patients because cure is improbable. Earle et al. (2008) reviewed aggressive cancer care near the end of life. Patients with various malignancies continued to receive intensive chemotherapy within 14 days of death in 17.1% of patients, and approximately 10% of patients remained hospitalized in the last month of life. The hematologic malignancies, such as AML and MDS, were most strongly associated with aggressive care. Additional findings included underutilization of hospice services; the National Cancer Policy Board (1999) defined this as poor-quality of care, when practices of known effectiveness are infrequently used.

Acute myeloid leukemia and high-risk MDS in older patients have a grim prognosis for several reasons. First, intensive chemotherapy is difficult for older individuals to survive because of comorbidities, decreased clearance of chemotherapy from renal effects of aging, and poor tolerance of bacterial and fungal infections (Eleni, Nicholas, & Alexandros, 2010). Older AML patients do not respond to intensive chemotherapy, when compared to their younger counterparts from an increased proportion of unfavorable karyotype abnormalities in chromosomes 5, and 7, and complex chromosomal rearrangements in older AML patients. Karyotyping, also known as cytogenetics, grow from bone marrow aspirates to evaluate for acquired chromosomal abnormalities (Knipp, et al. 2007). Cytogenetic analysis depends on cells that are undergoing cell division, or mitosis. Abnormal acquired chromosomal changes in the older patients often translate into resistance to intensive chemotherapy (Applebaum, et al., 2006). Other factors that have been associated with resistance to chemotherapy in the older AML patients include the evolution of AML from antecedent hematologic disorders such as MDS, the presence of dysplastic changes, the frequent expression of the multidrug resistance phenotype and the involvement of more primitive progenitors in the leukemic process (Applebaum, et al., 2006).

Limited information is available concerning QOL for older AML and high-risk MDS patients (Sekeres, et al., 2004; Stone, 2002; Alibhai, et al., 2009). To date, the primary objective of clinical trials has been evaluation of response to treatment, length of hospitalization, overall survival, and the biology of the disease (Estey, 2009). Quality of life has been the secondary focus of a few clinical trials, utilizing various instruments (Joly, Vardy, Pintilie, & Tannock, 2007). Quality of life becomes the focus of treatment when cure is impossible. If two treatments are equally efficacious, the one that results in a more favorable QOL should be chosen.

Quality of Life

Quality of life is a subjective, personal experience. The most accurate measurements for QOL come from the patient (Gotay, Kawamoto, Bottomley, & Efficace, 2008). There is agreement concerning the multidimensional aspect of QOL; however, which dimensions to include in QOL assessments vary. Domains evaluated in QOL are physical, psychological, functional, and social. Some models include spiritual and emotional as separate domains (Harris, et al., 2010). In 1994, the World Health Organization (WHO) defined QOL as “individuals’ perceptions of their position in life in the context of the culture and the value system in which they live and in relation to their goals, standards, and concerns” (WHO, Definition section, para. 1). Six domains of QOL are in the WHO definition including physical health, psychological health, and levels of independence, social relationships, environmental features, and spiritual concerns.

Intensive chemotherapy is less effective for older AML patients and is associated with significant toxicity resulting in fewer older patients receiving treatment. These small numbers make it difficult to evaluate response to treatment and QOL during the treatment (Fröhling, et.al, 2006). Older AML and high-risk MDS patients also have higher rates of recurrent leukemia after achieving remission with intensive chemotherapy (Löwenberg, et al., 2010), and greater comorbidity (Rao & Cohen, 2004). On the opposite spectrum of treatment options, Koreth and colleagues (2011), found that reduced intensity stem cell transplant offered a life expectancy benefit, with adjustment for quality survival.

Statement of the Problem

Acute myeloid leukemia and high-risk MDS are hematologic malignancies that occur most frequently in the seventh and eighth decades of life. Without treatment, AML and high-risk

MDS are associated with a poor prognosis, with median survival of five to twelve months for high risk MDS, and eight months for AML. With treatment, survival is improved; but cure is rare, with five-year survival rates of less than 10%. Therefore, the goal of treatment is to improve QOL, and palliate symptoms. Unfortunately, QOL is not routinely evaluated. It is important to improve QOL in older AML patients by identification of the factors that contribute the most to improved QOL, because cure is improbable. Equally important is the need to identify treatments that tend to worsen QOL, to prevent unnecessary suffering. Definitive evidence is not available. Studies are needed which compare QOL with different treatment approaches, intense versus non-intensive, and the variables which predict for QOL with different approaches to treatment.

Statement of the Purpose

The purpose of this observational longitudinal cohort study is to evaluate the impact of different treatments on QOL and evaluate predictors of QOL for older AML and high-risk MDS patients. The independent variables that will serve as predictors of QOL are diagnosis, age, comorbidities, and fatigue. The dependent variable is QOL.

Specific Aims

This study addresses the following aims:

1. To compare the difference in QOL scores measured by the Functional Assessment of Cancer Therapy –Leukemia version for intensive chemotherapy, non-intensive therapy, and supportive care within 7 days of new treatment and one month after initiation of treatment in older patients with AML or high risk MDS.
2. To determine QOL predictors of AML and high-risk MDS from age, comorbidity, fatigue, and diagnosis.
3. To examine the moderating effect of treatment with age, comorbidity, and fatigue on QOL.

Definition of Relevant Terms

1. Acute myeloid leukemia- a clonal, malignant disease of hematopoietic tissues characterized by (1) accumulation of abnormal (leukemic) blast cells, principally in the marrow, and (2) impaired production of normal blood cells. Thus, the leukemic cell infiltration in marrow is accompanied, nearly invariably, by anemia, and thrombocytopenia. The absolute neutrophil count may be low or normal, depending on the total white cell count (Liesveld, & Lichtman, 2010). This includes the cytogenetic analysis, or the study of genetics at the chromosome level of the hematopoietic cells (Tsai, Manchester, & Elias, 2011).
2. High-risk MDS- myelodysplasia is a term used to encompass a spectrum of clonal (neoplastic) myeloid disorders marked by ineffective hematopoiesis (exaggerated marrow cell apoptosis), cytopenias, qualitative disorders of blood cells and their precursors, clonal chromosomal abnormalities, and a variable predilection to undergo clonal evolution to AML (Liesveld, & Lichtman, 2010). This includes the cytogenetic analysis, or the study of genetics at the chromosome level of the hematopoietic cells (Tsai, Manchester, & Elias, 2011).
3. Intensive chemotherapy- chemotherapy administered to induce bone marrow aplasia, which is administered in the hospital intravenously. This treatment requires a four to six-week hospitalization for transfusion and infection management (Estey, 2006).
4. Comorbidity- concomitant but unrelated pathological or disease process. In this study, the number of comorbidities is measured using the Charlson Comorbidity Index (American Heritage Medical Dictionary, 2007).
5. Hypomethylating agents- drugs that inhibits deoxyribonucleic acid methylation. Current approved medications include azacitidine and decitabine (Sekeres, et al., 2004).

6. Best supportive care- care given to improve the QOL of patients who have a serious or life-threatening disease. The goal of supportive care is to prevent or treat as early as possible the symptoms of a disease, side effects caused by treatment of a disease, and psychological, social, and spiritual problems related to a disease or its treatment. Best supportive care is also called comfort care, palliative care, and symptom management (National Cancer Institute, 2013).

Assumptions

Several assumptions of this study are implicit. First, patients will choose the best treatment if they know how it affects the quality of their survival. Next, the study setting influences QOL evaluations. Inpatients may rate their QOL differently than outpatients. In addition, patients will evaluate their QOL accurately and honestly, which provides QOL data for individuals with similar diagnoses considering treatment.

Significance of the Study

The significance of this study is that it provides information on QOL for patients with high-risk MDS and AML. Because of this study, when faced with treatment choices the patient and caregiver may have more information to guide the best treatment approach. In addition, valuable information was obtained from the QOL measures regarding how the individual factors, such as age, comorbidity, and level of fatigue affect QOL. Increased knowledge of the impact of the factors can guide further studies focused on areas that can improve QOL. The development of predictive QOL models and individual predictors of QOL can help patients and health care providers select the most appropriate, personalized treatment, and provide a foundation for future QOL research in this patient population.

CHAPTER TWO:

REVIEW OF LITERATURE

The purpose of this chapter is to review and synthesize the current evidence of the determinants of QOL of older patients with high-risk MDS and AML. Searches of Medline, CINAHL, and PubMed were conducted for each of the measured variables including age, fatigue, comorbidity, treatment, and QOL in patients with high-risk MDS and AML. Manual searches of article references were included for relevant studies to include in the literature review, including research studies published on QOL in high-risk MDS and AML in the last 10 years. Peer reviewed manuscripts with the key terms MDS, QOL, and AML were analyzed for content validity, scientific rigor, and relevance to the current investigation. Then, the additional variables of age, co-morbidities, and fatigue were searched in combination with cancer and QOL. First, the theoretical framework is introduced; it guided integration of the variables of interest into QOL for patients with high-risk MDS and AML. Subsequently, empirical studies related to high-risk MDS and QOL were synthesized and highlight the current knowledge of QOL in AML and high-risk MDS. Finally, knowledge gaps are identified and the identification of where additional research is needed.

Theoretical Background

There is agreement concerning the multidimensional aspect of QOL, and that individuals are the best judges of their QOL. However, which dimensions to include in QOL assessments vary. Domains commonly evaluated include physical, psychological, functional, and social. Cella and colleagues (1993) included emotional well-being, social/family well-being, functional

well-being, and physical well-being in the Functional Assessment of Cancer Therapy (FACT). In 1994, the WHO defined QOL as “individuals’ perceptions of their position in life in the context of the culture and the value system in which they live and in relation to their goals, standards, and concerns” (WHO, Definition section, para.1). Six domains of QOL are in the WHO definition, including physical health, psychological health, and levels of independence, social relationships, environmental features, and spiritual concerns.

Age for High-Risk MDS and AML Patients

Both AML and MDS are malignancies primarily of older people. The peak incidence of AML is 67 years (SEER, 2015). Similarly, MDS occurs most commonly at 60-69 years (Shadduck, Latsko, Rossetti, Haq, & Abdulhaq, 2007). Survival rates are inferior in the greater than 60 age group for AML. It is unclear why survival rates are inferior, but the inability for older patients to tolerate the treatment has been proposed as an explanation for inferior survival rates. Special consideration is necessary when treating older patients with chemotherapy because of deterioration in organ function associated with advanced age (Lichtman, & Boparai, 2008). In addition, there are age-related changes in the metabolism of medications that require dose modifications. Anthracyclines, key drugs in the treatment of AML, require dose adjustment in patients greater than 60 years because of the association with cardio toxicity (Wojtacki, Lewicka-Nowak, & Les´niewski-Kmak., 2000). This dose modification affects survival. An explanation for poorer outcomes in older patients is the association between older age and poor performance status, comorbidities, treatment related AML (from prior chemotherapy or radiation), and most important, specific cytogenetic abnormalities (Applebaum et al., 2006; Wheatley, et al., 2009). Age has been studied as a prognostic indicator for survival, and to help determine the most appropriate therapy (Walter, Othus, Borthakur, et al., 2010). Thus far, evidence could not be

found for how age predicts QOL in patients with AML and MDS. Age is a major consideration for determining appropriate treatment, because advanced age adversely affects survival with conventional, intense chemotherapy.

Selecting effective treatment for AML and MDS in the elderly remains a challenging task. The biology of AML in older patients is different from patients younger than 60 years. Older AML patients have unfavorable chromosomes in the cytogenetic analysis of their bone marrow, which means they have more aggressive AML that is notoriously resistant to standard chemotherapy (Applebaum, et al., 2006). In addition, MDS is a disease almost entirely of elderly patients. When the disease progresses to AML, it is usually resistant to standard chemotherapy (Walter, et al., 2012).

Fatigue for High-Risk MDS and AML Patients

Patients with AML and MDS typically present to the healthcare system with symptoms related to anemia (Estey, 2012; Balducci, 2006). Other common problems for MDS and AML patients are bone marrow failure, and resultant complications (Estey, 2012). Profound fatigue, recurrent infections, bleeding, bruising, and shortness of breath are symptoms reported by MDS patients (Hofmann, & Koeffler, 2005). Steensma et al. (2008) in a 120- question Internet survey of 359 respondents reported excessive fatigue as the most common symptom reported by MDS patients. Fatigue had a negative impact on QOL, not correlated with hemoglobin levels. Instruments used in the Internet survey included the FACT-Anemia and the Brief Fatigue Inventory (BFI). Similarly, Schumacher, Kessler, Buchner, Wewers, & Van de Lou (1998) conducted prospective, repeated measures, longitudinal study to determine QOL for patients undergoing chemotherapy, according to the German AML Cooperative Group. Quality of life was measured at 12 different time points using the European Organisation for Research and

Treatment of Cancer Quality of Life Questionnaire –Core 30 (EORTC QLQ- C30; Aaronson et al., 1993). Sixty-one patients enrolled during the first 30 months of the study. Only 28 patients were alive, and able to complete all 12 measurements. For the patients who survived the treatment, emotional functioning and social functioning improved significantly by the end of treatment. In addition, fatigue was closely related to QOL, as measured by the EORTC QLQ-C30 subscale for fatigue, with QOL declining as fatigue increased. This study also found fatigue to have a low correlation with hemoglobin level. Oliva et al. (2011) conducted a prospective observational study to investigate changes in QOL scores and their association with therapy and survival in elderly patients with AML. One-hundred and thirteen patients enrolled. Forty-eight patients received intensive chemotherapy, and 65 received palliative treatment. Two different QOL instruments were administered, which included the EORTC QLQ-C30 and a health-related QOL questionnaire for patients with hematologic diseases named QOL-E. Survival was independently predicted by QOL-E functional ($p=0.002$) and EORTC QLQ-C30 physical ($p=0.030$) scores. In multivariate analysis both hemoglobin and age independently predicted fatigue ($R^2 0.114, P=0.001$) and ($R^2 0.066, P=0.01$) respectively. From these studies, there is evidence that fatigue is a rational predictor of QOL for AML and high-risk MDS.

Comorbidities and QOL

With advancing age the number and severity of comorbidities increase, and makes treatment decisions more difficult (Applebaum et al., 2006). It also makes teasing out the etiology of symptoms complicated. Wedding et al. (2007) evaluated global QOL in 477 patients to measure how functional impairment and co morbidity influence QOL. From this group, 195 were cancer patients aged 60 years or older (group A), 152 were cancer patients below the age of 60 years (group B), admitted as inpatients for chemotherapy initiation and 130 patients were

aged 60 years or older admitted for disorders unrelated to cancer (group C). The EORTC QLQ-C30 measured QOL. The Karnofsky Performance Scale (KPS) and the Instrumental Activities of Daily Living (IADL) scale measured functional status. Finally, the Cumulative Illness Rating Scale assessed comorbidity. In this study, the IADL and KPS independently contributed to global QOL, with patients experiencing lower scores for IADL and KPS having decreased global QOL scores. In addition, comorbidity contributed to global QOL in elderly cancer patients.

Oliva et al. (2011), in a prospective observational study evaluated changes in QOL scores and their association with therapy and survival in elderly patients with AML. The analysis included comorbidity data. Concomitant disease was any clinical illness that required a specific and prolonged treatment. In a sample of 113 elderly patients, 68 (60.1%) had a concomitant disease that required treatment. Fifteen percent (17/113) of the AML patients had more than one comorbidity. Concomitant diseases were arterial hypertension (29 patients), ischemic cardiovascular disease (20 patients), diabetes (18 patients), chronic respiratory disease (9 patients), and chronic gastrointestinal disease (6 patients). The combination of age and comorbidities impacted treatment decisions with a palliative approach chosen for 77% of patients over 70 years and for 48% of those under 70 years with concomitant diseases ($P=0.032$). For patients without comorbidities, age did not influence treatment decisions. Concomitant illnesses were associated with decreased survival, with median survival of 33 weeks (95% CI: 15–52 weeks), which was significantly shorter than that of patients without concomitant diseases (median not reached; $P=0.014$). However, QOL data were not provided for comorbidities because this was not the focus of the study. Rather, the focus was on survival of elderly AML patients. Small sample size is a limitation of this study.

QOL in Myelodysplastic Syndromes

The literature has limited research on QOL and AML/high-risk MDS. The majority of studies separate QOL evaluation of MDS from AML. Acute myeloid leukemia and MDS are bone marrow stem cell disorders that are treated similarly and have a limited life expectancy. The review of research begins with QOL in MDS and proceeds to AML QOL research.

The most recent nursing study on QOL in patients with MDS was qualitative, using a phenomenological approach (Thomas, 2012), because limited information was available about how MDS affects individuals living with the illness. The sample consisted of 70 patients recruited from an Internet posting on the Myelodysplastic Syndrome Foundation website. Five focus groups over five months convened in the United States. Individuals with a diagnosis of MDS were asked how the diagnosis affected their QOL. All focus group sessions were audio taped, transcribed, and coded for common themes.

Qualitative data from this study suggests that MDS has a substantial and negative impact on QOL for patients diagnosed with the disease. However, for the majority of the patients, the impact of MDS on physical well-being was minor. The impact of MDS on the functional abilities of the participants varied greatly, with some patients noting that they were no longer able to perform their normal activities, and other participants not reporting any limitations in their functional abilities. A diagnosis of MDS negatively affected emotional well-being, with patients voicing significant anxiety concerning the uncertainty of their prognosis and treatments, and receiving very limited teaching and emotional support from the health care team. For spiritual well-being, the majority reported a positive impact, with a need for reprioritization of values with a life limiting illness. Recommendations from the study included a more comprehensive approach to the care of MDS patients that includes nursing, behavioral medicine/psychology, and

social work. Suggestions were made for further studies to explore the impact of MDS on QOL in more detail to target interventions to assist patients coping with a complex, chronic malignancy (Thomas, 2012).

Steensma et al. (2008) conducted a study to quantify the burden of fatigue and other disease-associated symptoms in a large group of patients with MDS treated at multiple institutions and how they influenced QOL. The sample consisted of 359 patients recruited from the MDS Foundation by way of the Internet. The Charlson Comorbidity Index, Brief Fatigue Inventory, FACT-Anemia, and the Godin Leisure Time Activity Score measured fatigue, comorbidities, functional capacities, and other activities. The instruments were available on the Internet from January through October 2006. Patients were asked to complete the questions only once. From these surveys, 65% of patients reported having received blood products at some point since their MDS diagnosis. Excessive fatigue was the most common symptom (89%) reported by patients with MDS. Other problems included bruising/bleeding (55%), night sweats (43%), bone pain (39%), fevers (28%), skin rash (25%), undesired weight loss (25%), and recurrent infections (20%). Myelodysplastic syndrome impaired patients' ability to work. Disability due to MDS diagnosis was reported at 30%. As expected in this age group, 60% of the patients were "retired." Scores on QOL tools were markedly inferior to the general population. For FACT-Anemia, MDS patients scored a standardized mean of 50.5, compared to 77.1 for controls (where 100 is best possible QOL); $p < 0.0001$. The findings were similar for fatigue measurement. From this study, it was clear that patients with MDS experience debilitating fatigue that interferes with their ability to work. In addition, many of the patients with MDS were receiving active treatment for their MDS, illustrating the inadequacy of therapy in relieving symptoms associated with the disease process. It is also difficult to tease apart the symptoms due to treatment versus MDS.

Another important finding from this Internet study was the weak correlation between fatigue and hemoglobin levels. This study provided evidence that patients with MDS have significant symptoms that negatively affect QOL.

Azacitidine is an active treatment for MDS patients used to improve blood counts and prevent disease progression. In a phase III clinical trial, Kornblith et al. (2002) evaluated the impact of azacitidine on the QOL of 191 patients with MDS. Patients were randomized to receive either azacitidine as a subcutaneous injection seven days every four weeks, or supportive care. Crossover was allowed from the supportive care arm to azacitidine arm with disease progression. Measurement of QOL was conducted by phone interviews at baseline, and on days 50, 106, and 182. The EORTC QLQ-C30 and Mental Health Inventory were administered as the QOL measure. Patients treated with azacitidine experienced statistically significant improvements in fatigue, physical functioning, dyspnea, positive affect, and psychological distress. The greatest improvements were in fatigue and psychological state. Also noted was disease response, and delayed progression to AML, or death compared to the supportive care arm.

Despite encouraging treatment results, MDS negatively influences QOL of patients, according to Thomas (2012). The most common symptom reported by MDS patients is fatigue, which is not totally explained by anemia. In addition, as noted by Steensma et al. (2008), there are several other symptoms that patients report as negatively influencing QOL. Many symptoms are related to bone marrow failure, such as bleeding from thrombocytopenia, and the need for frequent transfusions with blood for anemia, and treatment for infections from neutropenia (Greenberg, et al. 2011). However, psychosocial factors play a considerable role in QOL for MDS patients. According to Thomas (2012), uncertainty concerning the disease and treatment

negatively impact QOL with patients reporting receiving limited emotional support and education from the healthcare team.

QOL in AML

Limited information is available concerning QOL for older AML patients. To date, the primary objective of clinical trials has been evaluation of response to treatment, length of hospitalization, overall survival, and the biology of the disease. Quality of life has been the secondary focus of many clinical trials, utilizing various instruments (Joly, Vardy, Pintilie, & Tannock, 2007). Without a uniform definition or tool for measurement for QOL, it is difficult to compare results between studies (Grant & Sun 2010). Patients can make more informed decisions regarding therapy with QOL data. It is reasonable that if two treatments are equally effective in treating AML or MDS, the one that results in a more favorable QOL would be chosen.

Clinical trials have evaluated various treatments in an attempt to improve overall survival in elderly patients with AML (Baron & Storb, 2007; Kantarjan et al. 2006; Sekeres et al., 2004). The impact of the various treatments on various conceptualizations of QOL was also assessed during these trials. In a prospective, randomized clinical trial by Lowenberg et al. (1989) survival was compared between two treatment approaches in 60 AML patients 65 years or older. The first treatment approach consisted of giving immediate intensive chemotherapy early in the course of the illness, known as arm A. The second treatment approach, arm B, consisted of a “wait and see” approach that included best supportive care. Chemotherapy was administered to patients in the “wait and see” group if their condition deteriorated rapidly, and treatment was thought necessary. The number of days spent in the hospital was used as a surrogate marker for QOL, which is not a measurement for QOL. Overall survival duration for patients treated on arm A

was significantly ($p=0.15$) longer than the survival in arm B (21 weeks versus 11 weeks). The percentage of days spent in the hospital was 55% in arm A, and 50% in arm B. However, there are obvious flaws in the definition and measurement of QOL. In addition, by waiting until the patients in the “wait and see” group were more ill, they naturally would be less likely to respond to treatment.

In a prospective, longitudinal study, Sekeres and colleagues (2004) examined the decision making considerations and QOL of 43 older adults with AML and advanced MDS in choosing between intensive chemotherapy (IC) and non-intensive chemotherapy (NIC). Patients were enrolled upon presentation to the participating institutions. Baseline questionnaires were completed prior to starting treatment, or within one day of starting IC. For the NIC group, questionnaires were completed at baseline and at two and six weeks of enrollment. The FACT both general and anemia specific measurements, and a shortened version of the Geriatric Depression Scale (GDS) were also administered. The FACT-Anemia is a QOL instrument that contains a general section (FACT-G), with four domains assessing physical well-being, social/family well-being, emotional well-being, and functional well-being (Cella, 1997). Within all measures except the GDS, higher scores indicate a better QOL. Patients choosing IC were younger, with a median age of 66 years than those choosing NIC, with a median age of 76 years. Baseline QOL scores and prevalence of depression were similar for both groups. Quality of life scores significantly deteriorated in the intensive chemotherapy group during the second week for the General FACT and Short Form 12 physical scores, which measures perceptions of physical functioning and not QOL. For the NIC group, the scores remained stable for QOL. By week 6, which correlated with hospital discharge, the IC group, as measured by physical functioning, had improved. Mortality rates at six weeks were similar between the two groups (Sekeres et al.,

2004). By one year, five patients from each group remained alive. In the IC group, QOL physical scores were negatively impacted during the time of hospitalization, which correlated with time of treatment with IC. This suggests that a less intense, outpatient approach could maintain QOL without negatively impacting survival because the survival rates between the two groups were similar at one year for this sample.

Kantarjian et al. (2006) compared treatment with decitabine, a hypomethylating agent, in patients with MDS to best supportive care in a phase III randomized control trial. A total of 170 patients were randomized to receive decitabine every six weeks or best supportive care.

Following review by an expert pathology group outside the study institution, a portion of the MDS patients were reclassified as having AML. The median age of patients was 70 with a range from 30-85 years. Quality of life was evaluated using the EORTC QLQ-C30. This instrument incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea, and vomiting), and a global health and QOL scale, with higher scores correlating with a better QOL. Evaluations were performed for QOL at the end of each treatment cycle. When compared to the supportive care group, the decitabine arm of treatment demonstrated a statistically significant superior QOL score in global health ($p < 0.05$ at the end of cycles two and four), fatigue subscale ($p < 0.05$ at the end of cycles two, four, five, and six), and dyspnea subscale ($p < 0.05$ at the end of all six cycles).

In an observational study by Alibhai et al. (2007), the effect of IC on QOL and functional status of 65 elderly AML patients was compared to NIC treatment. The age range for the NIC was 66-86 years with a mean age of 76.9 years. The IC group had a similar age range of 61-84 years with a mean age of 70.4 years. Quality of life and functional status were assessed at baseline, one month, four months, and six months in newly diagnosed AML aged 60 years or

older. The decision to treat with IC versus NIC was made by the physician based on clinical presentation. Quality of life was measured using the EORTC QLQ-C30. The FACT Fatigue subscale was used to investigate fatigue. Results for measurements of fatigue were reported in a separate manuscript. Quality of life was not inferior in the group that received NIC.

In a much larger study, Juliusson et al. (2009) retrospectively evaluated 2767 patients with AML diagnosed from 1997-2005 through the Swedish Acute Leukemia Registry. Early death rates (within 30 days of diagnosis) were lower with intensive treatment despite poor performance status at the time of diagnosis. Long-term survivors, not defined by the investigators, were found among elderly patients treated with IC. Recommendations were for treating elderly AML patients up to 80 with IC. This is contrary to recommendations from previous studies and emphasizes the ambiguity in treating older AML patients.

From an investigation by Oliva et al. (2011), QOL was identified as a prognostic factor for survival. In a prospective, observational study, 113 patients greater than 60 with AML completed two QOL instruments at diagnosis for all patients. The two instruments utilized were the EORTC QLQ C-30 and a health-related QOL questionnaire for patients with hematologic diseases (QOL-E). At diagnosis, patients were noted to have decreased general QOL-E (median QOL-E standardized score 54, interquartile range 46-70; median EORTC global score 50, interquartile range 41-66). The treating physician assigned most patients an Eastern Cooperative Oncology Group performance status score, which was favorable. These scores did not correlate with the patients' self-report of QOL. Survival was independently predicted by QOL-E functional ($P=0.002$) and EORTC QLQ-C30 physical function ($P=0.030$) scores when age and comorbidities were factored out. This has practice implications because therapy decisions are commonly based on the treating physicians' assignment of a performance status, as opposed to

the patient. From these results, further research should be performed to confirm the findings. This provides evidence for the valuable information that can be obtained from QOL assessments.

Conclusions

In summary, this chapter presented a review of the literature related to QOL in older patients diagnosed with AML and high risk MDS. The conceptual framework that guided the design of the study was introduced as well as the major variables proposed to be predictors of QOL for high-risk MDS and AML patients. Age and comorbidities are the primary variables for treatment determination in high risk MDS and AML, especially when looking for curative therapy with hematopoietic stem cell transplant. Fatigue is the most frequently reported symptom in MDS, and identified as a predictor of QOL in previous studies. This needs more close examination in AML. Currently, there is a need for better QOL data including predictors so that patients can make informed decisions concerning available treatments and their impact on QOL. In the next chapter, the design and methods of the study are presented, with a description of the instruments utilized to measure QOL, comorbidities, and fatigue.

The conceptual model that guided this study (Figure 1) symbolizes the effects of age, diagnosis, comorbidity, and fatigue on QOL, and the moderating effect of treatment on QOL. The variables on the left of the model guide treatment decisions, and were chosen for their logical association with QOL. A comparison of QOL between treatment approaches appears on the right side of the model.

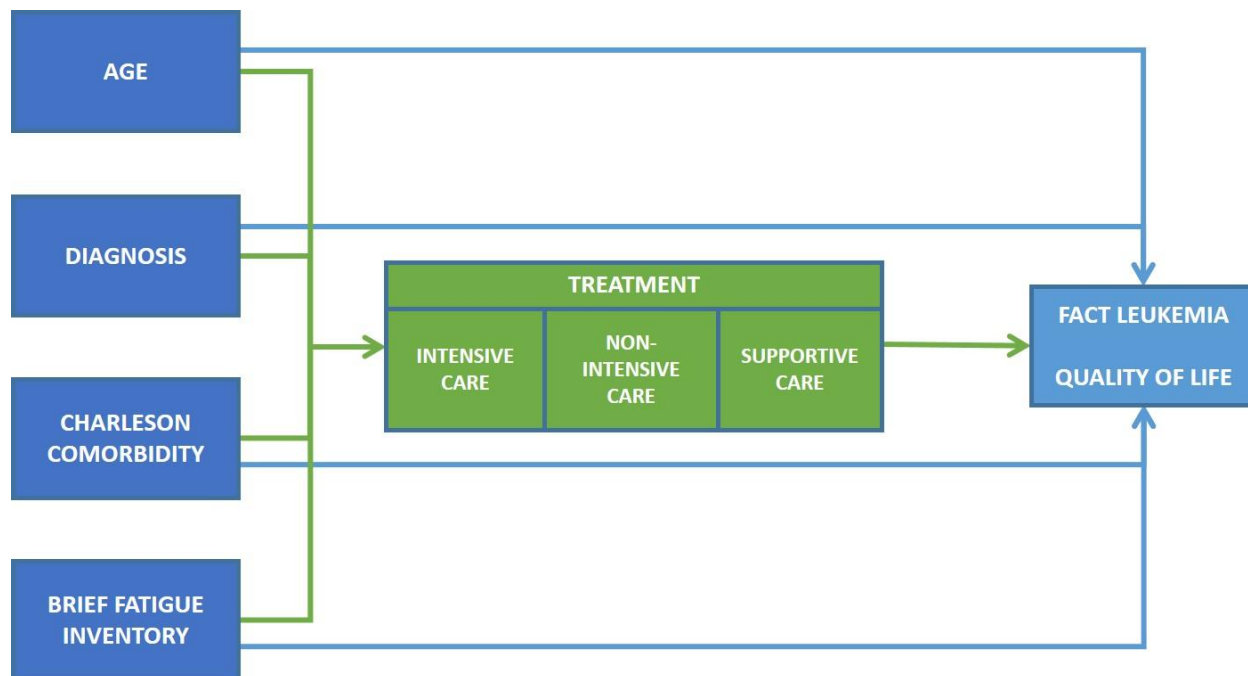


Figure 1: Conceptual Model for the Study

CHAPTER THREE:

METHODS

In this chapter, the methods for the study are presented. This includes the design of the proposed study, sample, setting, data collection, measures, and plan for data analysis. The process for protecting human subjects is described.

Study Design

The study utilized an exploratory observational, longitudinal cohort design comparing QOL between two treatment approaches in patients 60 years of age and older with high-risk MDS and AML at two time points. The plan was to compare three treatment groups, but low accrual for the supportive care group restricted evaluation to two groups. A randomized controlled trial was not possible because physicians base treatment decisions on prognostic indicators and patient preference. In addition, there would be ethical concerns for randomization to specific treatment versus supportive care given the diagnosis of the participants.

Setting

The setting for the study was Moffitt Cancer Center and Research Institute in the department of Malignant Hematology. Moffitt is a National Cancer Institute designated Comprehensive Cancer Center that sees more than 100 new leukemia and high-risk MDS patients annually. The collection of data occurred in both outpatient and inpatient setting.

Sample

Recruitment of 85 patients with high-risk MDS and AML occurred at the time of appointments in the Hematology Clinic or during admission to Moffitt Cancer Center for

treatment evaluation of AML or high-risk MDS. This number of participants was based on power analysis. A sample size of 100 was suggested for five predictors with an effect size of .14, and an alpha of .05, with 80% power. Inclusion criteria include individuals 60 years of age and older with confirmed diagnosis of high-risk MDS or AML based on bone marrow pathology reports. High-risk MDS and AML were treated as one group. Patients were able to read, write, and speak English, were oriented to person, place, and time, and were willing to participate.

Measures

FACT-Leukemia

Quality of life was assessed at the time of enrollment and within at least one month of enrollment using the FACT-Leu. The domains included in the FACT-Leu are social/family well-being, physical well-being, functional well-being, and relationship with their physician (Cella, Tulsky, & Sarafian, 1993). The instrument consists of 28 Likert-type items, with patients asked to respond to each item with a score of zero to four, with zero indicating “not at all” and four meaning “very much.” Scores range from zero to 112 with higher scores indicating better QOL. A subscale specific for leukemia is added to the general scale. The leukemia subscale consists of 17 items, with a score range of zero to 68. Evidence for convergent validity of the general instrument was provided by Cella et al. (1993) based on data from 854 patients with various cancer diagnoses when compared with the Functional Living Index-Cancer (FLIC), with a Pearson product moment correlation of 0.79. Victorson, Barocas, Song and Cella (2008) provided evidence of reliability in a study where 344 publications were reviewed based on predetermined criteria. Seventy-eight published studies reported Cronbach’s alpha reliability coefficients. They found the FACT-General score reliability to be .88 with a range of subscales from .71 to .83.

Brief Fatigue Inventory

Fatigue was measured using the Brief Fatigue Inventory (Mendoza, Wang et al. 1999) at the time of enrollment in the study. This is a one page, nine-item questionnaire, which measures fatigue on a scale of zero to ten, with zero indicating no fatigue, and ten representing the worst fatigue that a person can imagine. This instrument has been used in acute and chronic leukemia (Chang et al., 2008; Shanafelt et al., 2007). There is evidence of construct validity of the instrument by factor analysis. Evidence of concurrent validity of the instrument was demonstrated by correlating the Brief Fatigue Inventory with other fatigue measures such as Profile of Mood States. Cronbach's alpha coefficient for internal consistency reliability was very high (alpha =0.95 and 0.96) (Mendoza, Wang et al., 1999).

Charlson Comorbidity Index

Measurement of number of comorbidities was performed at the time of enrollment using the Charlson comorbidity index (Charlson, Pompei, Ales, & MacKenzie, 1987). The electronic version of the tool was utilized (Charlson, Szatrowski, Peterson, & Gold, 1994). This tool was developed to assign a number that estimates risk of mortality related to number and severity of comorbidities. It is the most commonly used instrument for evaluation of comorbidities in elderly patients with hematologic malignancies (Extermann, &Wedding, 2011). The index encompasses 19 medical conditions weighted one to six with total scores ranging from 1 to 37. A single score, which is a sum of the weighted conditions, is tallied. There is evidence of reliability of the instrument with inter-rater reliability, reported at 0.74 among a cohort of older general oncology patients and 0.945 within a group of elderly breast cancer patients (Extermann, 2000). Test-retest reliability was also excellent, ranging from 0.92 among surgical patients and 0.86 among the previously mentioned group of elderly oncology patients.

Demographic Data

Baseline information obtained on all subjects included age, as measured by date of birth, and diagnosis from pathology report including chromosome analysis by G-banding technique, and by fluorescence in situ hybridization. Demographic data collected also included gender, marital status, level of education, income level, religious ceremony attendance on a scale of zero to four, and designation of intensive, non-intensive, or supportive care treatment.

Procedures

Approval was obtained from the Scientific Review Committee (SRC) at Moffitt followed by approval from the Institutional Review Board (IRB) of the University of South Florida. Patients were approached by the principal investigator at their scheduled appointment or during the first week of their admission to obtain the informed consent, and administer the questionnaires. Eligibility was confirmed by utilization of a checklist. A quiet, comfortable room was provided for completing the questionnaires. A copy of the consent form was provided to participants to keep for future reference, and contact information was within the consent form. It was emphasized that participation was voluntary, and their care would not be altered, regardless of study participation. Demographic data collection was captured using a two-page sheet completed by each patient. The FACT-Leu and Brief Fatigue Inventory were administered within the first week of treatment. The second FACT-Leu was administered at least four weeks later. Data was stored in a locked filing cabinet in a locked office in the Hematology Clinic. All data was extrapolated to Excel spreadsheets coded only by patient identification number to ensure patient confidentiality. A patient identification number was assigned to each subject to assure confidentiality. The FACT-Leu scores were designated as FACT-Leu 1 and FACT-Leu 2 to identify first and second measurement.

Data Analysis

Data was analyzed using Statistical Package for the Social Sciences version 22 for Windows (IBM, Armonk, NY). Data was screened for outliers, and missing data. Descriptive statistics was used to describe study participants and study variables. Level of significance was set at an alpha level of .05. The following aims were addressed and data synthesized for conclusions.

Aim One: QOL from Week 1 to Week 4

To compare the difference in QOL scores measured by the FACT-Leu for intensive chemotherapy, non-intensive therapy, and supportive care within 7 days of new treatment and one month after initiation of treatment in older adults with AML or high-risk MDS. Repeated measures analysis of variance was ran as group, time, and group by time, with follow up tests for significant findings for the interaction. The groups included intensive versus non-intensive and supportive care. Time was the first and second measurements of FACT-Leu.

Aim Two: Predictors of QOL

To determine QOL predictors of AML and high risk MDS from age, comorbidity, fatigue, and diagnosis. Bivariate correlations were analyzed between age, Charlson Comorbidity Index, Global Fatigue Score, and FACT-Leu, time 1. Diagnosis, as a categorical variable, was recoded as a dummy variable and contrasted all groups with high risk MDS.

Aim Three: Moderators of QOL

To test the moderating effect of treatment with age, comorbidity, and fatigue on QOL. Linear regression was performed to determine the moderating effect of treatment on age, comorbidity, and fatigue on the second QOL score.

CHAPTER FOUR:

RESULTS

The results of the study are provided in this chapter. Descriptive statistics of the sample are presented, separated by treatment group allocation. This is followed by means and standard deviations of all instruments with study totals divided by treatment group. Finally, the three aims of the study are statistically analyzed with tabled results and explanation.

Sample

The sample was comprised of 85 subjects recruited from the Malignant Hematology Program at Moffitt Cancer Center. The suggested sample size was not achieved due to slow accrual with one investigator, and time sensitive enrollment; within one week of treatment. Statistically significant findings were obtained with the sample of 85. All participants had a confirmed pathologic diagnosis of AML or high risk MDS. The sample was predominantly white, male, retired, middle class, and attended religious activities at least twice per month (Table 1).

Demographic data was divided by treatment groups to determine if the groups varied demographically. The intense treatment group had slightly more women than the non –intense and supportive care groups (Table 1). The supportive care group was comprised of five women, with varying ethnic backgrounds, and included no men. There were approximately equal numbers of participants at the lowest level and highest level of income reported. The majority of

participants reported income between \$25,000 and \$99,000 annually. Most (73%) were retired (Table 1).

Table 1. *Frequencies and Percentages of Demographic Variables.*

Variable	Intense (n=46)		Non-intense (n=34)		Supportive care (n=5)		Total (n=85)	
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
Male	29	63	27	80	0	0	56	66
White	44	96	33	97	3	60	80	94
Married	30	65	26	77	5	100	61	72
Retired	31	67	28	82	4	80	63	74
Middle class	27	59	20	59	3	60	50	60
High school education	20	44	17	50	2	40	39	46
College education	20	44	16	36	3	60	40	47
Monthly religious activity	23	50	14	41	3	60	40	47

The age of the sample was constrained to patients 60 years of age and older. Among the three groups, the mean age was slightly lower for the induction group by four years; however, the range was similar (Table 2), ranging from the sixties to the 80's. Each treatment group had patients in the lower and higher ages.

Table 2. *Mean, Range, and Standard Deviation of Age for Groups.*

Age	Intense	Non-intense	Supportive Care	Total
Mean	70	74	74	72
Range	61-83	60-88	63-86	60-88
Standard deviation	6.18	6.97	8.56	6.85

Categorical variables and age were analyzed between the intense and non-intense groups, using Chi-square and paired t-test for age. The groups were not significantly different from each other. Supportive care was not included because of low accrual (Table 3).

Table 3. Chi Square and Paired t-Test for Demographic Variables Between Intense and Non-Intense Treatment for Subjects Who Completed Both QOL Measures (N=67).

Variable	Chi square	t	df	p
Age	-	1.972	65	.580
Gender	2.288	-	1	.130
Ethnicity	2.847	-	3	.416
Marital status	7.255	-	4	.123
Employment	2.756	-	5	.738
Income	2.638	-	3	.451
Education level	7.261	-	8	.509
Religious activity	3.975	-	5	.553

Diagnosis varied between the three treatment groups. Five categories of diagnosis were coded with results reported (Table 4). Participants with AML were treated with both intense and non-intense treatment. A higher percentage (24%) of patients with high risk MDS were treated with a non-intense therapy, and supportive care (40%). Four different diagnosis categories were among the supportive care group. Patients with AML received all three types of treatments. The highest accruing groups were AML with MDs changes (37%) and AML (34%).

Table 4. Frequencies of Diagnoses.

Diagnosis	Intense (n=46)	Non-intense (n=34)	Supportive Care (n=5)	Total (n=85)
AML	16	12	1	29
AML with MDS changes	23	8	-	31
AML-therapy related	3	2	-	5
AML from MPN*	2	1	1	4
MDS- High risk	2	8	2	12
MDS- therapy related	-	3	1	4

*MPN-Myeloproliferative neoplasm

The three instruments used in this study were the Charlson Comorbidity Index, the Brief Fatigue Inventory, and the FACT-Leu. Results for the means and standard deviations of the three instruments, separated by treatment group are reported in Table 5.

Table 5. Means and Standard Deviations of Instruments

Variable	Intense (n=46)	Non-intense (n=34)	Supportive care (n=5)	Mean Total (n=85)
CCI ^{a*}	1.15 ± 1.28	1.56 ± 1.70	0.6 ± .89	1.28 ± 1.45
GFS ^{b*}	4.34 ± 2.52	4.23 ± 2.21	5.92 ± 2.09	4.39 ± 2.39
FL1 ^{c*}	117.53 ± 24.01	116.36 ± 27.45	106.37 ± 12.15	116.41 ± 25.00
FL2 ^{d*}	126.06 ± 22.60 (n=41)	113.76 ± 24.70 (n=26)	108.50 ± 6.35 (n=4)	120.64 ± 23.54 (n=72)

a*- Charlson Comorbidity Index, b*-Global Fatigue Score c*- FACT-Leu 1, d* -FACT-Leu 2

Descriptive Data

Aim One: QOL from Week 1 to Week 4

The comparison between two groups, intense and non-intense treatment is presented in Table 6 on FACT-Leu scores taken at two time points. The supportive care group was not included in the analysis because of low accrual. Repeated measures analysis of variance was utilized to determine main effects of time, group, and group by time interaction. An interaction of group by time was statistically significant ($p = .040$).

Table 6. Repeated Measures Analysis of Variance of Group, Time, and Group by Time (N=67) for QOL Scores.

Effect	MS	df	F	p
Time	147.107	1	.449	.505
Group	654.160	1	1.477	.229
Group x Time	1491.211	1	4.555	.040

Follow up tests were performed to determine the effect of time for each of the treatment groups. The results are reported in Table 7. There was a significant improvement in QOL scores between the first and second measurement in the induction group ($p=.020$).

Table 7. Repeated Measures Analysis of Variance for Time by Groups.

Effect	MS	df	F	p
Intense treatment	1634.17	1	5.76	.020*
Non-intense treatment	317.54	1	0.773	.388

*Significant at .05 level

Aim Two: Predictors of QOL

This indicates that as the level of fatigue increased, QOL scores decreased (Table 8).

Table 8. Correlation of Predictors with QOL from FACT-Leu 1 (N=85).

Variable	r	P
Age	.13	0.12
Charlson Comorbidity Index	.04	0.35
Global Fatigue Score	-.69	< 0.001

Diagnosis is a categorical variable with six levels that were recoded as dummy variables. Each diagnosis was contrasted with high-risk MDS (not therapy related) and was correlated with QOL (Table 9). Diagnosis was not significantly correlated with QOL.

Table 9. Correlation of Diagnosis with QOL from FACT-Leu 1 (N=85).

Variable	r	P
AML	.141	.100
AML from MDS	-.023	.418
AML Therapy Related	.120	.137
AML from Myeloproliferative Neoplasm	-.116	.145
Therapy Related MDS	-.034	.378

Regression analysis was performed to determine if the second measure of QOL could be predicted from the first QOL score, and then age, comorbidity, and fatigue were entered into the model (Table 10). Scores from the FACT-Leu 1 were a significant predictor of the second QOL measure ($P < 0.001$), which explained 19.6% of the variance. With the addition of age, comorbidity, and fatigue, the variance explained increased to 22.6%, but was not statistically significant.

Table 10. *Regression of Predictor Variables on QOL on FACT-Leu 2.*

Variable	B	Standard error of B	Beta	t	P
FACT LEU1	.422	.106	.433	3.99	< 0.001
Age	-.666	.434	-.185	-1.533	.130
Comorbidity	.790	1.834	.051	.431	.668
Global Fatigue	-.054	1.532	-.005	-.035	.972

Aim Three: Moderators of QOL

Linear regression was performed with a plug in application by Hayes (2013) to determine the moderating effect of treatment with age, co-morbidity, and fatigue on QOL. In Table 11, the moderating effects of age with type of treatment analysis are displayed. The results were statistically significant, indicating that when combining all three variables, the model predicts QOL ($p=0.049$).

Table 11. *Linear regression FACT-Leu 2 from Moderator, Type of Treatment, and Age.*

Model		df	Mean Square	F	p
1	Regression	3	538.95	2.764	.049 ^b

a. Dependent Variable: Time 2 FACT-Leu Total

b. Predictors: Moderator, type of treatment, age

The coefficients for type of treatment, age, and moderator effect are reported in Table 12. The moderator was not significant ($p=.066$). Type of treatment was significant ($p=.043$). This indicates the main effects of treatment on QOL scores, which was previously shown in Aim One. The intensive treatment group had an improvement in FACT-Leu 2 scores.

Table 12. *Coefficients^a for Type of Treatment, Age, and Moderator Effects on QOL.*

Model	Unstandardized Coefficients			
	<i>B</i>	<i>Std. Error</i>	<i>t</i>	<i>p</i>
1 (Constant)	307.995	95.659	3.219	.002
Age	-2.376	1.350	-1.760	.083
Type of treatment	-130.960	63.411	-2.065	.043
Moderator	1.657	.882	1.872	.066

a. Dependent Variable: Time 2 FACT-Leu

Multiple linear regression was performed to determine if the second measure of the FACT Leu could be predicted from the type of treatment, Charlson Comorbidity Index, and the moderator. Results indicated that the score from the second QOL measure could not be predicted from the moderator variable ($p = .140$).

Regression was performed to determine if the type of treatment and fatigue with the moderator were significant predictors of the FACT-Leu 2. All three combined revealed a significant F ratio of 0.12 shown in Table 13. The coefficients in Table 14 indicate that the moderator variable was not significant ($p=.729$). The main effect of treatment was statistically significant ($p= .016$) and the main effect of fatigue was significant ($p = .014$) shown in Table 14. These results are consistent with prior results, which indicate the main effects of fatigue and treatment for predicting QOL scores.

Table 13. Regression of FACT-Leu 2 from Moderator, Type of Treatment, and Fatigue.

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	6231.364	3	2077.121	3.981	.012 ^b

a. Dependent Variable: Time 2 FACT-Leu

b. Predictors: (Constant), Fatigue-moderator, type of treatment, Global Fatigue Score

Table 14. Coefficients^a for Type of treatment, Fatigue, and Moderator.

Model	Unstandardized Coefficients		Standardized Coefficients	t	p
	B	Std. Error	Beta		
1 (Constant)	154.792	10.179		15.207	.000
Type of treatment	-14.477	5.831	-.291	-2.483	.016
Global fatigue	-3.189	1.267	-.297	-2.517	.014
Fatigue-moderator	-1.042	2.992	-.041	-.348	.729

a. Dependent Variable: Time 2 FACT-Leu total

CHAPTER FIVE:

DISCUSSION, IMPLICATIONS AND CONCLUSIONS

In this final chapter, the research results are synthesized with discussion of the findings from earlier studies. The purpose of this observational longitudinal cohort study was to assess how different treatment approaches influence QOL. The study also evaluated predictors of QOL for older patients with high-risk MDS and AML who are 60 years of age and older. Quality of life was measured using the FACT-Leu at two times points, before and one month following treatment. The sample from which the data were obtained is examined, along with descriptive statistics of the instruments. The findings for each aim are interpreted and potential explanations provided for the results to address the issue of how treatment impacts QOL for patients with high-risk MDS and AML. This is followed by implications, conclusions, and recommendations for future studies.

Sample

There were 85 subjects with a diagnosis of high-risk MDS or AML who were 60 years of age or older. This may have created a restricted range problem in the analysis. However, the majority of patients with these diagnoses are 60 years of age and older. This was a predominantly retired white male sample, with a medium level of income. Among the three groups, the range of ages was similar, with patients from the seventh and eighth decade represented in all three groups. Within the sample, there were six levels of diagnoses captured, with the most frequently occurring diagnoses being AML without prior bone marrow disorder and AML with MDS changes, which is consistent with what is reported in the literature

(Applebaum et al., 2006). Prior MDS is also one of the reasons that AML in the older population is difficult to treat when compared to AML in patients less than 60 years of age (Stone, 2002).

The sample for supportive care was too small to be included in the statistical analysis. One explanation for this problem is that Moffitt Cancer Center is a referral center for patients seeking treatment. Individuals who only want supportive care are not referred to Moffitt Cancer Center. More research is needed to evaluate QOL for patients only receiving supportive care.

Descriptive Data

Three instruments were used in the study to measure comorbidities, fatigue, and QOL. Treatment decisions are determined by the physician and patient based on comorbidities, and level of functioning at the time of evaluation for determination of treatment. Comorbidities for this study were measured using an online calculator for the Charlson Comorbidity Index. An unexpected finding was how similar the scores were for the Charlson Comorbidity Index across the three groups. Among the three groups, the comorbidity mean scores were 1.2 for intense treatment, and 1.6 for non-intense treatment. The lowest comorbidity score was in the supportive care group, at 0.6. This was contrary to prior research. Oliva et al. (2011) reported that a combination of age and comorbidities impacted treatment decisions with a palliative approach chosen for 77% of patients over 70 years, and for 48% of those under 70 years with concomitant diseases (P=0.032). A reason for the difference may be the instruments that were used to measure comorbidities. Comorbidity was defined as any clinical illness that required a specific and prolonged treatment.

Fatigue was measured using the Brief Fatigue Inventory, which gives a zero to 10 score. The Global Fatigue Scores were similar between the intensive and non-intensive groups, 4.3 and 4.2 respectively. The supportive care group had the highest GFS at 5.9, indicating that fatigue

was greater in the supportive care group, despite fewer comorbidities. Fatigue is poorly understood in MDS and AML; however, it is known to be one of the most debilitating symptoms reported in the literature, and negatively influences QOL (Meyers, et al., 2005). This may be due to limitations in normal activities due to overwhelming fatigue.

The focus of this study, QOL, was measured using the FACT-Leu. Each patient completed the 3-page questionnaire within the first week of starting treatment (FACT-Leu 1), and again at least one month following the first measurement (FACT-Leu 2). From FACT-Leu 1 to FACT-Leu 2 mean scores improved for the intense chemotherapy (mean =117.5 to 126.1). For the non-intense therapy the mean scores decreased (mean= 116.4 to 114.0), an unanticipated finding because patients were able to stay home with their families, as opposed to a one-month hospitalization. Next, the supportive care group, based on only four patients who completed both measures, improved from 106.4 to 108.5. Overall, the first measurement of QOL was similar between the induction and outpatient based treatment. However, the mean QOL score for the supportive care arm was lower by 10 points, and did not improve to meet the starting mean score for the induction or outpatient group by the second measure. Possible explanations for this result are discussed in the next section.

Aim One: QOL from week 1 to week 4

A comparison was made between two treatment approaches, intensive and non-intensive therapy. Supportive care was not included in the analysis because of low accrual with only four patients completing both measurements of QOL at two time points. Group by time repeated measures analysis of variance was used to compute the results in SPSS version 22. For the main effects of group and time, there was not a significant finding. The interaction of group by time was statistically significant ($p=.040$). Then to determine which group by time was significant,

follow up tests were performed of the intensive and non-intensive treatment groups. The intensive treatment by time was significant ($p = .020$), and the non-intensive treatment by time analysis was not statistically significant.

It was an unexpected finding that the most intense treatment, requiring a one-month hospitalization separated from the familiar comforts of home showed a statistically significant improvement in QOL at one month, while the non-hospitalized group did not. Subscale analysis was not performed to determine which areas of QOL were improved the most. The findings for the longitudinal inpatient, intensive chemotherapy treatment are new, and have not previously been documented. Sekeres (2004) compared intensive chemotherapy with non-intensive treatment approaches in 43 patients with AML, finding that QOL declined for the intensive chemotherapy group measure by the General FACT and Short Form 12 physical scores at week 2, but repeat measures for week 4 were not reported by these investigators. The time of measurement at 2 weeks is a disadvantage because it is when patients have the lowest blood counts, and symptoms may improve as the effects of the treatment abate with time. Thus, the difference in time of data collection for the current study likely accounts for the differences in results.

The subjects in the non-intensive treatment group did not change significantly in their QOL scores. Rather, they maintained their QOL. When previous comparisons were made between non-intense treatment and palliative care by Kornblith et al. (2002), patients who received outpatient based hypomethylating azacitidine had a statistically significant improvement in QOL. The measurement intervals were different compared to the current study, and was not compared to intensive treatment. Instead, the comparison arm was palliative care. The current study was limited by low accrual of patients receiving supportive care only.

Aim Two: Predictors of QOL

Regression analysis was performed to determine if age, co-morbidity, fatigue, or diagnosis helped predict QOL scores. For the first regression, 85 patients' results for the FACT-Leu 1 were entered, and regression was performed. The FACT-Leu 1 was a significant predictor of the FACT-Leu 2 score as might be expected ($p < .001$). Cancer diagnosis was not correlated with QOL score and was left out of the regression; this supported the idea of combining MDS and AML patients for this study. Next age, co-morbidity and fatigue were added to see if they significantly predicted QOL scores on the FACT-Leu 1. The best predictor of FACT-Leu 2 was FACT-Leu 1. Age, comorbidity, and fatigue were not statistically significant. This could be attributed to the lack of variance in age, Charlson Comorbidity Index, and the Global Fatigue Score.

Age and comorbidities were not helpful as far as determining QOL with various treatments. This could be related to the restricted range of ages, based on the purpose of the study, which limits variance in age by study design. In addition, the Charlson Comorbidity Index did not discriminate between subjects with symptomatic disease, and those with indolent comorbidities. Most patients had similar scores on the index, which did not allow for teasing apart the patients who were sicker from comorbid conditions to be able to predict QOL scores.

Aim Three: Moderators of QOL

Moderation of the variables was evaluated by performing regression analysis with a plug-in program by Hayes (2013). Each moderator was entered into a regression analysis with FACT-Leu 2 as the dependent variable. There was not a moderator effect of age with treatment (p value = .066). The main effect of treatment was significant ($p = .043$).

Comorbidity and the moderator of comorbidity with type of treatment was not a statistically significant predictor of QOL. Many treatment decisions are made based on the number and severity of comorbidities. In this study, comorbidities did not correlate with QOL scores, and did not help predict how treatment affected QOL.

The final moderator effect analyzed was fatigue with type of treatment. When checked individually with coefficients, the moderator effect was not statistically significant, but the individual variables, both the type of treatment and fatigue score were significant ($p=0.016$ and $p=0.014$). This reinforces previous findings that fatigue and type of treatment can predict QOL score (Alibhai, Leach, Kowgier, et al., 2007). Schumacher and colleagues (2002) found that fatigue was more closely associated with QOL than nausea and vomiting and lack of appetite with intensive chemotherapy. Fatigue, identified in this earlier study of 37 patients, was the most common symptom that occurred at baseline with all patients, and improved following treatment. This would suggest that fatigue is related to the disease process, and when the disease is treated QOL can be improved. Other less obvious factors may be involved, such as ongoing support and encouragement of the healthcare providers throughout the inpatient hospitalization, which may improve the emotional and physical health of the patient.

The results of this study have identified new findings about QOL and treatment in patients with AML and high-risk MDS. This is the first study which has shown that QOL of patients 60 years of age and older have a statistically significant improvement in QOL one month after completing intensive chemotherapy treatment. This measurement is taken at the end of a prolonged hospitalization, away from their normal routine and home. Improvement in QOL was not an anticipated finding, and may represent some underlying process that is not obvious, such as hope after completing treatment. Many patients fear dying, and may be relieved that they

survived the treatment long enough to return home. It may also reflect improvement in QOL that is relative to how inferior QOL was prior to treatment. Data was not obtained with regards to treatment response. This would be an important addition to future studies that evaluate QOL with various treatment approaches.

Another explanation for the improvement in QOL scores is the potential improvement in disease related symptoms, which are more immediate with intensive treatment. In contrast, less intensive, outpatient based therapy works over time, and at the end of only one month of treatment, disease modifying benefits have not yet been achieved. This may explain why the outpatient group had an overall stable QOL score. Conclusions cannot be drawn from the supportive care group, and low accrual is related to the setting for the study, a comprehensive cancer center. Patients who seek care at comprehensive cancer centers are usually interested in pursuing active therapy. If a comparison is to be made with supportive care, and alternative setting should be pursued, such as hospice, or a community cancer center.

Implications for Nursing

Fatigue was highly correlated with QOL score, and the information was easily obtained from a one-sheet questionnaire, which took approximately 3-5 minutes to complete. This is the focus for many patients, and should be routinely evaluated in clinical settings. Interventions can be tailored to improve aspects of fatigue that are not directly related to the disease, such as hydration and sleep patterns disrupted by worry.

The results of this study will be submitted for publication in the Oncology Nursing Forum. The results can be included in education of nurses for fatigue assessment and management. The NCCN guidelines include a section on cancer related fatigue that can be utilized for curriculum development for fatigue management in oncology patients. Nurses are in

a key position for educating and encouraging patients in management of fatigue to improve QOL.

Implications for Future Research

Nurse researchers can design future studies to focus on fatigue interventions, and systematically evaluate the responses. This could make an impact on QOL by targeting fatigue. In addition, a future study is needed that includes the supportive care group. Accrual was limited by the setting of the current study, which could be expanded to include community cancer centers and hospices. This study is limited by the predominantly white male sample. Additional studies should include a more diverse ethnic background, which includes equal representation of participants that exemplify the type of AML and high-risk MDS patients in the United States. In addition, the non-intensive treatment group was limited by inclusion of patients who were treated on clinical trials, as well as with hypomethylating agents. The experiences of these patients may have varied, and the current study was not designed to separate the subgroups within the non-intensive treatment group. An alternative research design suggestion is the limitation of the non-intensive group to hypomethylating treatment, such as decitabine and azacitidine. Additional QOL measurements at three months, and six months would provide information about how QOL changes with time. For the non-intensive treatment group, an expectation would be that their QOL would improve if additional measures were taken.

Study Limitations

The primary limitation of this study is sample size and composition. With larger numbers, there may have been moderating effects of treatment with age, comorbidity, and fatigue. In addition, this predominantly white, male group limits the generalizability of the findings. The supportive care group was small, with only five patients. Most patients seeking

care at a comprehensive cancer center are interested in pursuing active therapy instead of supportive care. This also limits the findings to other comprehensive cancer centers. The patient experience may differ in a community setting.

Conclusions

In conclusion, this study revealed that QOL was improved at one month for patients with AML or high-risk MDS who were treated with intense chemotherapy. For patients who were treated with non-intense therapy, QOL was stable at one month. Fatigue was identified as highly correlated with QOL, and is a predictor of QOL. Fatigue management is a recommended focus for future intervention studies. The significant predictor of the second QOL measure was the first QOL measure. Age, comorbidity, and fatigue with type of treatment failed to show a moderating effect on QOL. Future studies with larger numbers are recommended to confirm the findings and provide additional clinical information to help patients choose the treatment approach that matches their individual goals.

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APPENDICES

Appendix A: Institutional Review Board Approval



UNIVERSITY OF
SOUTH FLORIDA

December 18, 2013

Sara Tinsley, ARNP

H Lee Moffitt Cancer Center

Tampa, FL 33612

RE: **Expedited Approval for Initial Review**

IRB#: ProOOOI4329

RESEARCH INTEGRITY AND COMPLIANCE
Institutional Review Boards, FWA No. 00001669
12901 Bruce B. Downs Blvd., MDC035 • Tampa, FL 35612-4799

(813)974-5638 • FAX (SI 3) 974-7091

Title: Predictors of Quality of Life in Patients with AML and high

risk MDS

Study Approval Period: 12/18/2013 to 12/18/2014

Dear Ms. Tinsley:

On 12/18/2013, the Institutional Review Board (IRB) reviewed and **APPROVED** the above application and all documents outlined below.

Approved Item(s):

Protocol Document(s):

17606 2013.09.16 Revised protV2 clean

Consent/Assent Document(s)*:

14329 12-01-2QI3.doc Version I informed consent.pdf

*Please use only the official IRB stamped informed consent/assent document(s) found under the "Attachments" tab. Please note, these consent/assent document(s) are only valid during the approval period indicated at the top of the form(s).

It was the determination of the IRB that your study qualified for expedited review which includes activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the categories outlined below. The IRB may review research through the expedited review procedure authorized by 45CFR46.110 and 21 CFR 56.110. The research proposed in this study is categorized under the following expedited review category:

(7) Research on individual or group characteristics or behavior (including, but not limited to,

research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

As the principal investigator of this study, it is your responsibility to conduct this study in accordance with IRB policies and procedures and as approved by the IRB. Any changes to the approved research must be submitted to the IRB for review and approval by an amendment.

We appreciate your dedication to the ethical conduct of human subject research at the University of South Florida and your continued commitment to human research protections. If you have any questions regarding this matter, please call 813-974-5638.

Sincerely,



Kristen Salomon, Ph.D., Vice Chairperson
USF Institutional Review Board

Appendix B: Scientific Review Committee Approval

October 11, 2013

MOFFITT
CANCER CENTER

Sara Tinsley
H. Lee Moffitt Cancer Center & Research Institute 12902 Magnolia Drive Tampa, FL
33612

Dear Ms. Tinsley:

RE: MCC 17606 "Predictors of Quality of Life for High Risk MDS and AML Patients"

The Behavioral Subcommittee of the Scientific Review Committee (SRC) has reviewed your response dated 09/28/2013 for your research protocol. The revised protocol version 2 dated 09/16/2013 is approved as written for use at the Moffitt Cancer Center pending approval of the Institutional Review Board (IRB) and satisfaction of institutional operational and financial review requirements.

Please be aware that after you receive IRB approval, you must request study activation before you commence any study activities. Please contact PSO mailbox at PSQmailbox@moffitt.org to request study activation. That office will ensure that all applicable institutional reviews have been completed. You will then be issued an automated activation notification by email.

It is your responsibility to ensure that all Moffitt staff (nursing, pharmacy, data management, etc.) are informed and aware of the details of the project. The committee encourages the use of inservices for those projects that are complex or require special attention.

All changes made to protocols approved by the SRC must be submitted to the Protocol Review and Monitoring System office. Changes made to the protocol document require SRC review and approval. Minor changes (i.e. changes to personnel, non-scientific changes, changes that do not affect patient participation) will be expedited through the SRC review process.

If this project is not being managed by the Clinical Trials Office or Clinical Research Unit, then it is your responsibility to follow through with all requirements for submission to the IRB. All IRB approvals are required to be documented in Oncore, and all associated regulatory documentation (signed applications, IRB approval letters and IRB approved consent forms, etc.) are to be saved in the appropriate study folder in the e-binders directory at J:\ebinders.

Oncore is the Cancer Center's mechanism for submission and review of materials requiring Scientific Review (SRC) and Protocol Monitoring (PMC). If you need access to Oncore, please contact Jeryl Madden, Oncore Administrator, at 745-6964 for assistance.

Sincerely,



David Drobos, PhD.
Chair, Behavioral Sub-Committee Scientific Review Committee

Appendix C: Charlson Comorbidity Index

6/6/2015

Charlson combined age-comorbidity Index > Score Calculator

Age adjusted Charlson Comorbidity Index

Also available:

- Same tool using - Weighted Charlson Index (or design)
- CCI for use in

Age range

- <50
 - 50-59
 - 60-69
 - 70-79
 - 80-89
 - 90-99
-

1- AIDS (Not just HIV positive)

- Yes
 - No
-

2- Myocardial infarction (history, not ECG changes only)

- Yes
 - No
-

3- Congestive heart failure

- Yes
 - No
-

4- Peripheral vascular disease (includes aortic aneurysme ≥ 6 cm)

- Yes
 - No
-

5- Dementia

- Yes
 - No
-

6- Chronic pulmonary disease

- Yes
 - No
-

7- Connective tissue disease

<http://tools.farmacologiaclinica.info/index.php?sid=37148&lang=en&loadsecurity=>

1/3

Yes

No

8- Peptic ulcer disease

Yes

No

9- Moderate or severe renal disease

Yes

No

10- Leukemia (acute or chronic)

Yes

No

11- Malignant lymphoma

Yes

No

12- Malignant solid tumor

Metastatic

Non-metastatic¹

No

1. Exclude if > 5 years from diagnosis, Except malignant neoplasm of skin

13- Cerebrovascular disease

Hemiplegia

Without hemiplegia

No

14- Liver disease

Moderate or severe

Mild¹

No

1. Includes chronic hepatitis

15- Diabetes

- With end-organ damage¹
- Without end-organ damage²
- No

1. Retinopathy, neuropathy, nephropathy, or brittle diabetes
2. Excludes diet-controlled alone
-

Appendix D: Terms and Conditions for Use of Charlson Comorbidity Index

Categories Project Submit your calc Demo

pmidCALC.org

PMIDCALC

Copyrighted resources

Questionnaires are reproduced on this site as a public service for study and research purposes and not for financial gain.
At pmidCALC.org we always check carefully that no copyright is claimed over the questionnaires.
Nevertheless some questionnaires require training for their proper use or permission to be obtained before they can be used and sometimes it may be difficult to establish copyright over questionnaires which are often freely available in paper form (particularly if they have been amended).

If copyright holders object to their questionnaires being reproduced online by us, they can send us a removal request at admin@pmidcalc.org. If you suspect there is copyright infringing content in pmidCALC.org Website please report it using the same email address.

[Other Legal Statements](#)

2015 © PmidCalc Project | [Legal statements](#) | [Contact](#)

The information and calculators provided on this site are intended only as a general resource for clinicians and are not intended to reflect a standard of care or to replace individual professional judgment. In any case, please read our complete [disclaimer](#).

Appendix E: Demographic Questionnaire

DEMOGRAPHIC QUESTIONS

What is your month and year of birth? (MM/YYYY)

What is your gender?

- Male
- Female

Would you describe yourself as:

- American Indian / Native American
- Asian
- Black / African American
- Hispanic / Latino
- White / Caucasian
- Pacific Islander
- Other

Marital status

- Married
- Divorced
- Widowed
- Separated
- Never been married
- A member of an unmarried couple

How many children live in your household who are:

- Less than 5 years old?
- 5 through 12 years old?
- 13 through 17 years old?

How would you describe your current employment status?

- Employed full time
- Employed part time
- Unemployed / Looking for work
- Student
- Homemaker
- Retired
- Unable to work

What do you expect your family income from all sources before taxes to be?

- Under \$24,999
- \$25,000 - \$99,999
- Over \$100,000

What is the highest level of education you completed?

- Elementary school only
- Some high school, but did not finish
- Completed high school
- Some college, but did not finish
- Two-year college degree / A.A / A.S.
- Four-year college degree / B.A. / B.S.
- Some graduate work
- Completed Masters or professional degree
- Advanced Graduate work or Ph.D.

Apart from events such as weddings and funerals, how often do you attend religious services?

- More than once a week
- Once a week
- Once or twice a month
- A few times a year
- Never

Appendix F: Brief Fatigue Inventory

Brief Fatigue Inventory										
STUDY ID# _____						HOSPITAL# _____				
Date: ____/____/____						Time: _____				
Name: _____ <div style="display: flex; justify-content: space-around;"> Last First Middle Initial </div>										
Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the last week? Yes <input type="checkbox"/> No <input type="checkbox"/>										
1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW.										
<div style="display: flex; justify-content: space-between;"> 0 1 2 3 4 5 6 7 8 9 10 </div> <div style="display: flex; justify-content: space-between;"> No Fatigue As bad as you can imagine </div>										
2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during past 24 hours.										
<div style="display: flex; justify-content: space-between;"> 0 1 2 3 4 5 6 7 8 9 10 </div> <div style="display: flex; justify-content: space-between;"> No Fatigue As bad as you can imagine </div>										
3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours.										
<div style="display: flex; justify-content: space-between;"> 0 1 2 3 4 5 6 7 8 9 10 </div> <div style="display: flex; justify-content: space-between;"> No Fatigue As bad as you can imagine </div>										
4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your:										
A. General Activity										
<div style="display: flex; justify-content: space-between;"> 0 1 2 3 4 5 6 7 8 9 10 </div> <div style="display: flex; justify-content: space-between;"> Does not Interfere Completely Interferes </div>										
B. Mood										
<div style="display: flex; justify-content: space-between;"> 0 1 2 3 4 5 6 7 8 9 10 </div> <div style="display: flex; justify-content: space-between;"> Does not Interfere Completely Interferes </div>										
C. Walking ability										
<div style="display: flex; justify-content: space-between;"> 0 1 2 3 4 5 6 7 8 9 10 </div> <div style="display: flex; justify-content: space-between;"> Does not Interfere Completely Interferes </div>										
D. Normal work (includes both work outside the home and daily chores)										
<div style="display: flex; justify-content: space-between;"> 0 1 2 3 4 5 6 7 8 9 10 </div> <div style="display: flex; justify-content: space-between;"> Does not Interfere Completely Interferes </div>										
E. Relations with other people										
<div style="display: flex; justify-content: space-between;"> 0 1 2 3 4 5 6 7 8 9 10 </div> <div style="display: flex; justify-content: space-between;"> Does not Interfere Completely Interferes </div>										
F. Enjoyment of life										
<div style="display: flex; justify-content: space-between;"> 0 1 2 3 4 5 6 7 8 9 10 </div> <div style="display: flex; justify-content: space-between;"> Does not Interfere Completely Interferes </div>										
<small>Copyright 1999 The University of Texas M. D. Anderson Cancer Center All rights reserved.</small>										

BFI - English - Formatted March 16, 2008

Appendix G: Authorization to Use Brief Fatigue Inventory

From: symptomresearch [symptomresearch@mdanderson.org]
Sent: Friday, July 26, 2013 10:17 AM
To: Tinsley, Sara M.
Cc: symptomresearch
Subject: RE: Order Form for Department of Symptom Research Assessment Tools

Hello Sara,

I have attached the BFI as you requested. Please let me know if you have any questions. Thank you for your interest in the BFI.

The email that is sent with the tool is the authorization letter for all the non-funded academic research, clinical practice or educational purpose.

Regards,

Mary Samad

Appendix H: FACT Leukemia Questionnaire

FACT-Leu (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

<u>PHYSICAL WELL-BEING</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

<u>SOCIAL/FAMILY WELL-BEING</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box <input type="checkbox"/> and go to the next section.</i>					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Leu (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<u>EMOTIONAL WELL-BEING</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness.....	0	1	2	3	4
GE3	I am losing hope in the fight against my illness.....	0	1	2	3	4
GE4	I feel nervous.....	0	1	2	3	4
GE5	I worry about dying.....	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

<u>FUNCTIONAL WELL-BEING</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
GF1	I am able to work (include work at home).....	0	1	2	3	4
GF2	My work (include work at home) is fulfilling.....	0	1	2	3	4
GF3	I am able to enjoy life.....	0	1	2	3	4
GF4	I have accepted my illness.....	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now.....	0	1	2	3	4

FACT-Leu (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<u>ADDITIONAL CONCERNS</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
ERM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
P2	I have certain parts of my body where I experience pain....	0	1	2	3	4
ERM2	I am bothered by the chills	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
LEU1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin).....	0	1	2	3	4
TH1	I bleed easily	0	1	2	3	4
TH2	I bruise easily	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
EMT6	I get tired easily	0	1	2	3	4
C2	I am losing weight.....	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
An7	I am able to do my usual activities.....	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU5	I feel uncertain about my future health	0	1	2	3	4
LEU6	I worry that I might get new symptoms of my illness.....	0	1	2	3	4
ERM9	I have emotional ups and downs	0	1	2	3	4
LEU7	I feel isolated from others because of my illness or treatment.....	0	1	2	3	4

Appendix I: FACT-Leu Licensing Agreement

FUNCTIONAL ASSESSMENT OF CHRONIC ILLNESS THERAPY (FACIT) LICENSING AGREEMENT

July 24, 2013

*The Functional Assessment of Chronic Illness Therapy system of Quality of Life questionnaires and all related subscales, translations, and adaptations (“FACIT System”) are owned and copyrighted by David Cella, Ph.D. The ownership and copyright of the FACIT System - resides strictly with Dr. Cella. Dr. Cella has granted FACIT.org (Licensor) the right to license usage of the FACIT System to other parties. Licensor represents and warrants that it has the right to grant the License contemplated by this agreement. Licensor provides to **Moffitt Cancer Center** the licensing agreement outlined below.*

This letter serves notice that **Moffitt Cancer Center** and all its affiliates (as defined below) (“COMPANY”) are granted license to use the **English** version of the **FACT-Leu** in one study.

“Affiliate” of (COMPANY) shall mean any corporation or other business entity controlled by, controlling or under common control with (COMPANY) For this purpose “control” shall mean direct or indirect beneficial ownership of fifty percent (50%) or more of the voting or income interest in such corporation or other business entity.

This current license extends to (COMPANY) subject to the following terms:

- 1) (COMPANY) agrees to provide Licensor with copies of any publications which come about as the result of collecting data with any FACIT questionnaire.
- 2) Due to the ongoing nature of cross-cultural linguistic research, Licensor reserves the right to make adaptations or revisions to wording in the FACIT, and/or related translations as necessary. If such changes occur, (COMPANY) will have the option of using either previous or updated versions according to its own research objectives.
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- 4) In all publications and on every page of the FACIT used in data collection, Licensor requires the copyright information be listed precisely as it is listed on the questionnaire itself.
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- 6) This license is only extended for use on the internet on servers internal to (COMPANY). This FACIT license may not be used with online data capture unless specifically agreed to by Licensor in writing. Such agreement will only be provided in cases where access is password protected.
- 7) Licensor reserves the right to withdraw this license if (COMPANY) engages in scientific or copyright misuse of the FACIT system of questionnaires.
- 8) There are no fees associated with this license.

Appendix J: Informed Consent

Study ID: Pro00014329 Date Approved: 12/18/2013 Expiration Date: 12/18/2014



Informed Consent to Participate in Research Information to Consider Before Taking Part in this Research Study

IRB Study # Pro00014329

You are being asked to take part in a research study. Research studies include only people who choose to take part. This document is called an informed consent form. Please read this information carefully and take your time making your decision. Ask the researcher or study staff to discuss this consent form with you, please ask him/her to explain any words or information you do not clearly understand. We encourage you to talk with your family and friends before you decide to take part in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.

The study risk is considered minimal since the patient will participate in completing questionnaires about quality of life at their convenience. The subject matter is sensitive and provoking since the subjects are being asked to describe their personal feelings regarding the diagnosis and treatment of a cancer with a very poor prognosis.

Please tell the study doctor or study staff if you are taking part in another research study.

We are asking you to take part in a research study called:

What are the predictors of quality of life for adults with high risk myelodysplastic syndrome or acute myeloid leukemia?

The person who is in charge of this research study is Sara Tinsley. This person is called the Principal Investigator. However, other research staff may be involved and can act on behalf of the person in charge. Sara Tinsley is a student in the nursing PhD program at the University of South Florida. She is being guided in this research by Dr. Susan McMillan.

The research will be conducted at Moffitt Cancer Center in Tampa, Florida.

Purpose of the study

The purpose of this study is to:

- Seek information from the patient to help health care providers guide older adults with acute myeloid leukemia and high risk myelodysplastic syndrome in choosing treatment based on quality of life data.

IRB Number: Pro00014329
IC Adult Minimal Risk - SB Rev:9-3-2010



IRB Consent Version 1 12/01/2013
Page 1 of 6

- This study is being conducted by a student as part of their dissertation which is required for graduation

Study Procedures

If you take part in this study, you will be asked to:

- Review the informed consent
- Complete a quality of life questionnaire that takes approximately one hour of time.
- Complete the questionnaire at the time of a regular clinic visit at Moffitt Cancer Center.
- Results will be analyzed, and not linked to participants by name, but numbers.
- Sign the informed consent prior to completing the questionnaire.
- Only the principal investigator will have access to the results.

Total Number of Participants

About one hundred and twenty individuals will take part in this study at USF.

Alternatives

You do not have to participate in this research study.

Benefits

We are unsure if you will receive any benefits by taking part in this research study.

Risks or Discomfort

The following risks may occur:

- Since this is an illness that can be life threatening, discussion about the illness and treatment may be upsetting. Support through social workers and counselors will be made available to each participant following the interview if requested.

Compensation

You will not be compensated for participation in this study.

Cost

There will be no additional costs to you as a result of being in this study. However, routine medical care for your condition (care you would have received whether or not you were in this study) will be charged to you or your insurance company. You may wish to contact your insurance company to discuss this further.

Authorization to Use and Disclose Protected Health Information

Who will see your health information?

In this research study, we use and share your health information to the extent authorized (permitted) by you. We know that this information is private. The federal privacy regulations of the Health Insurance Portability & Accountability Act (HIPAA) protect your identifiable health information. If you authorize us to use your information we will protect it as required by the law.

Research at Moffitt Cancer Center is conducted jointly with the University of South Florida. By signing this form, you are permitting Moffitt Cancer Center and the University of South Florida to use personal health information collected about you for research purposes. You are also allowing Moffitt Cancer Center to share your personal health information with individuals or organizations other than USF and Moffitt Cancer Center who are also involved in the research and listed below.

Who will disclose (share), receive, and/or use your information?

To conduct this research, USF and the people and organizations may use or share your information. They may only use and share your information:

- With the people and organizations on this list;
- With you or your personal representative; and
- As allowed by law.

In addition to the people and organizations listed below in the Privacy and Confidentiality section of this document, the following groups of people may also be able to see information about you and may use the information to conduct the research:

- The medical staff that takes care of you and those who are part of this research study;
- Each research site for this study. This includes the research and medical staff at each site and USF;
- The designated peer review committees such as Scientific Review Committee

Who else can use and share this information?

Anyone listed above may use consultants in this research and for the purpose of this study, may share your information with them. If you have questions about who they are, you should ask the study team. Individuals who receive your health information for this research study may not be required by the HIPAA Privacy Rule to protect it and may share your information with others without your permission. They can only do so if permitted by the laws governing them. For example, the study sponsor may share your information with others. If the sponsor or others share your information, your information may no longer be protected under the HIPAA Privacy Rule.

How will my information be used?

By signing this form, you are giving your permission to use and/or share your health information as described in this document for any and all study/research related purposes. Your authorization to use your health information will not expire unless you revoke it in writing.

As part of this research, USF may collect, use, and share the following information:

- Your whole research record
- All of your past, current or future medical and other health records held by USF, other health care providers or any other site affiliated with this study. This includes, but is not limited to, HIV/AIDs, mental health, substance abuse, and/or genetic information.

For the Research Participant (you) to complete:

I am asking USF and the researchers not to include, use, or share the following health information

in this research (if blank, then no information will be excluded):

Your Rights:

You can refuse to sign this form. If you do not sign this form you will not be able to take part in this research study and therefore not be able to receive the research related interventions. However, your health care outside of this study and benefits will not change.

How Do I Withdraw Permission to Use My Information?

You can revoke this form at any time by sending a letter clearly stating that you wish to withdraw your authorization to use of your health information in the research. If you revoke your permission:

- You will no longer be a participant in this research study;
- We will stop collecting new information about you;
- We will use the information collected prior to the revocation of your authorization. This information may already have been used or shared with other, or we may need it to complete and protect the validity of the research; and
- Staff may need to follow-up with you if there is a medical reason to do so.

To revoke this form, please write to:

Principal Investigator

For IRB Study # **Pro00014329**
University of South Florida
12901 Bruce B. Downs Blvd., MDC 22
Tampa, FL 33612-4799

While we are conducting the research study, we cannot let you see or copy the research information we have about you. After the research is completed, you have a right to see the information about you, as allowed by USF policies.

Privacy and Confidentiality

We will keep your study records private and confidential. Certain people may need to see your study records. By law, anyone who looks at your records must keep them completely confidential. The only people who will be allowed to see these records are:

- The research team, including the Principal Investigator, study coordinator, research nurses, and all other research staff.
- Certain government and university people who need to know more about the study. For example, individuals who provide oversight on this study may need to look at your records. This is done to make sure that we are doing the study in the right way. They also need to make sure that we are protecting your rights and your safety.

- Any agency of the federal, state, or local government that regulates this research. This includes the Department of Health and Human Services (DHHS) and the Office for Human Research Protection (OHRP)
- The USF Institutional Review Board (IRB) and its related staff who have oversight responsibilities for this study, staff in the USF Office of Research and Innovation, USF Division of Research Integrity and Compliance, and other USF offices who oversee this research.

We may publish what we learn from this study. If we do, we will not include your name. We will not publish anything that would let people know who you are.

Voluntary Participation / Withdrawal

You should only take part in this study if you want to volunteer. You should not feel that there is any pressure to take part in the study. You are free to participate in this research or withdraw at any time. There will be no penalty or loss of benefits you are entitled to receive if you stop taking part in this study.

New information about the study

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

You can get the answers to your questions, concerns, or complaints

If you have any questions, concerns or complaints about this study, or experience an adverse event or unanticipated problem, call Sara Tinsley at 813-340-3864

If you have questions about your rights as a participant in this study, general questions, or have complaints, concerns or issues you want to discuss with someone outside the research, call the USF IRB at (813) 974-5638.

Consent to Take Part in this Research Study

and Authorization to Collect, Use and Share Your Health Information

It is up to you to decide whether you want to take part in this study. If you want to take part, please sign the form, if the following statements are true.

I freely give my consent to take part in this study and authorize that my health information as agreed above, be collected/disclosed in this study. I understand that by signing this form I am agreeing to take part in research. I have received a copy of this form to take with me.

Signature of Person Taking Part in Study

Date

Printed Name of Person Taking Part in Study

Statement of Person Obtaining Informed Consent

I have carefully explained to the person taking part in the study what he or she can expect from their participation. I hereby certify that when this person signs this form, to the best of my knowledge, he/she understands:

- What the study is about;
- What procedures/interventions will be used;
- What the potential benefits might be; and
- What the known risks might be.

I can confirm that this research subject speaks the language that was used to explain this research and is receiving an informed consent form in the appropriate language. Additionally, this subject reads well enough to understand this document or, if not, this person is able to hear and understand when the form is read to him or her. This subject does not have a medical/psychological problem that would compromise comprehension and therefore makes it hard to understand what is being explained and can, therefore, give legally effective informed consent. This subject is not under any type of anesthesia or analgesic that may cloud their judgment or make it hard to understand what is being explained and, therefore, can be considered competent to give informed consent.

Signature of Person Obtaining Informed Consent / Research Authorization

Date

Printed Name of Person Obtaining Informed Consent / Research Authorization