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Due to a Bone Marrow Transplant, is Loneliness From Hospital Isolation a Predictor of Health Outcomes

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DUE TO A BONE MARROW TRANSPLANT, IS LONELINESS FROM HOSPITAL ISOLATION A PREDICTOR OF HEALTH OUTCOMES?

By

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Abstract

Previous research indicates loneliness affects physiological and quality of life outcomes in oncology populations. However, minimal research has been conducted specifically on bone and blood marrow transplant (BMT) patients (Knight et al., 2013). To further explore this issue, we conducted a preliminary study to examine the relationship of loneliness with quality of life, immunological functioning, and other health indicators at six months post-transplant in BMT patients. The Functional Assessment of Cancer Therapies–BMT (FACT-BMT) was used to measure QOL and the UCLA Loneliness Scale Version 3 was used to assess general loneliness and loneliness experienced during hospitalization. We found that experiencing loneliness during hospital stay and experiencing loneliness in general was negatively associated with overall quality of life six months after a BMT. Specially, hospital loneliness was associated with poorer social well-being and poorer functional well-being; and loneliness in general was associated with poorer social well-being. In addition, loneliness during hospitalization was related to difficulty managing disease symptoms six-months after a transplant. Hospital loneliness was associated with higher neutrophil counts to monocyte counts 30 days after BMT, which is an indicator of poorer overall survival rate. However, loneliness during hospital stay was not associated with neutrophil to lymphocyte ratio. These results indicate that there is a relation between loneliness experienced during hospitalization and immunological functioning which may adversely impact recovery from a bone marrow transplant.

Keywords: loneliness, oncology, bone marrow transplant, health outcomes, immune components

Due to a Bone Marrow Transplant, Is Loneliness from Hospital Isolation a Predictor of Health Outcomes?

A bone marrow transplant (BMT) is an arduous medical procedure which carries a high risk of mortality and morbidity post-transplant due to health complications and isolation. In comparison to other oncology populations, there is minimal research that determines the relations between immune function, psychosocial factors, and clinical outcomes in BMT populations. These relationships may be significant due to the importance of prompt immune recovery and immune regulation in preventing infections and reducing morbidity and mortality (Costanzo, Juckett, & Coe, 2013). Costanzo et al. (2013) suggests that potential mechanisms of psychosocial factors influence immune processes which are relevant to post bone marrow transplant outcomes. Stable social support throughout the transplant process has been linked to positive health outcomes (Frick, Ramm, Bumeder et al., 2006; Lim & Zebrack, 2006; Rodrigue, Pearman, & Moreb, 1999) as well as predicts overall survival, higher quality of life, decreased depression rates, and decreased psychosocial morbidity (Cooke, Gemmill, Kravits, & Grant, 2006; Grassi, Indelli, Marzola et al., 1996; Jacobsen, Sadler, Booth-Jones et al., 2002; Jenks Kettmann & Altmaier, 2008; Lloyd-Williams & Friedman, 2001; Rodrigue et al., 1999; Widows, Jacobsen, Booth-Jones et al., 2005).

Loneliness and Social Connection

Loneliness is experienced throughout the general population, gradually diminishing during middle adulthood and increasing again around the age of 70 (Heinrich & Gullone, 2006; Pinquart & Sorensen, 2001; Theeke, 2009; Weeks, 1994). Despite varying loneliness definitions, all share three major themes in that loneliness involves: (1) inadequate social relationships, (2) personal experience, and (3) distressing and unpleasant experience of loneliness (Peplau &

Perlman, 1982, p. 3). In their study, Peplau and Perlman (1982) focus on the concept of loneliness as a distressing feeling that accompanies the perception that one's own social needs are lacking in quantity and quality (Hawkley & Cacioppo, 2010). Similar to perceived social isolation, individuals who live relatively lonely lives may not experience loneliness; however, individuals who appear to have active social lives may experience feelings of loneliness (Pinquart & Sorensen, 2001). Experiencing loneliness has evolved as a signal for behavior change, similar to hunger, thirst, or physical pain, with individuals motivated to maintain and form intimate social connections (Cacioppo & Hawkley, 2009 & Cacioppo et al., 2006).

Social connections and relationships are fundamental components to positive psychological and physical wellbeing (Cacioppo et al., 2000). According to the Evolutionary Model conceptualized by Cacioppo and Hawkely (2005), unsafe feelings arise when an individual experiences loneliness. These feelings stimulate the survival mechanism, intensifying the sensitivity to threats from all types of relationships. This embedded survival instinct focuses on threats that initiate anxiety and detrimental interactions, allowing individuals to reduce short term damage of undesirable interactions. However, there is a risk of self-defeating hostility with individuals finding personal fault and blame (Cacioppo & Hawkley, 2005; Rotenberg, 1994). When experiencing loneliness, greater susceptibility to threats, rejection, and feelings of insecurity may occur.

Loneliness is associated with social withdrawal, depression, shyness, pessimism, alienation, and low positive affect (Ernst & Cacioppo, 1999). Moreover, lonely individuals are more likely to have poorer social skills, reduced social support, lower surgency, lower emotional stability, and lower conscientiousness. In addition, loneliness has been found to be related to fear of negative evaluation, higher anxiety, negative mood, and anger (Cacioppo et al., 2006).

According to Cacioppo, Hawkley, & Thisted (2010) loneliness predicts depressive symptoms, however depressive symptoms do not predict loneliness.

As individuals create better social connections they begin to alleviate the sense of threats and social pain, allowing true relations to form with others. In being open and socially connected, a creation of genuine connection and real relationships might arise for an individual. When feelings of sociality are satisfied, free of social pain, individuals experience better health. Moreover, feelings of connection reduce agitation, stress, and generally alleviates hostile feelings and depression, affecting health in positive ways (Cacioppo & Patrick, 2009).

Loneliness and Health

The Loneliness Model (Cacioppo & Hawkley, 2009; Cacioppo, Hawkley, Ernst et al., 2006) incorporates the Evolutionary Model by Cacioppo and Hawkely (2005) and wherein they stated that perceived social isolation is similar to feeling unsafe, beginning a cycle of social threat feelings to the environment. Accordingly, lonelier individuals view their surroundings as more threatening, expecting greater undesirable social interactions, and recalling greater undesirable social information. Negative and undesirable social expectations have a tendency to provoke behavior in others that confirms the negative social expectations of lonelier individuals. These expectations initiate a self-fulfilling prophecy whereby lonely people purposely detach from potential social relations due to the belief that social distancing is attributable to others and surpass one's own control (Newall, Chipperfield, Clifton et al., 2009). Unfortunately, this loop of self-reinforcement is accompanied by feelings of anxiety, hostility, low self-esteem, pessimism, and stress (Cacioppo & Hawkley, 2009) which exemplifies a dispositional tendency that stimulates behavioral and neurobiological mechanisms that contribute to undesirable health outcomes (Hawkley & Cacioppo, 2010).

Social isolation has been related to adverse impacts on health and well-being (Alpass & Neville, 2003; Berkman, 1995; Freyne, 2005; Hawton, 2010; MuCulloch, 2001). Specifically, social isolation and loneliness are associated with poorer physical well-being, mental health (Cacioppo et al., 2000; Ernst & Cacioppo, 1999; Lui, 2007; Perkins, 1991), personality disorders, psychoses (DeNiro, 1995; Richman, & Sokolove, 1992;), impaired cognitive functioning, cognitive decline over time (Gow et al., 2007; Tilvis et al., 2004; Wilson et al., 2007), and increased depressive symptoms (Cacioppo, et al., 2006; Heikkinen & Kauppinen, 2004; Segrin, 1999; Wei, Russell, & Zakalik, 2005). Overall, having a poor social network and experiencing high levels of loneliness are related to poorer quality of life (Ekwall, Sivberg, Hallberg, 2004). Loneliness appears to have a significant impact on physical well-being which has been linked to immune stress responses and worse cognition over time (Luanaigh & Lawlow, 2008).

In a study conducted by Cacioppo et al. (2000) on young and older adults, there were no differences between high or low scores on the UCLA Loneliness scale and their healthy lifestyle behaviors (e.g. exercise, use of tobacco and alcohol). However, nonlonely individuals were better at reducing stress than lonelier individuals. Stress can exhibit harmful side effects to internal organs and can cause lonely individuals health to rapidly deteriorate compared to their nonlonely counterparts (Cacioppo, 2003).

Research provides evidence that the concept of social support lowers morbidity and mortality rates in oncology populations, cerebrovascular populations, and cardiovascular populations (Uchino, 2006). There are well-supported associations between the presence of supportive, nurturing relationships and positive health outcomes (Berkman, 1995; House, Landis, & Umberson, 1988; Uchino, Cacioppo, & Kiecolt-Glaser, 1996). Moreover, there is a complex linkage between health and social networks, suggesting that social networks may play a key role

in individuals' well-being. However, reliable and valid survey measures are lacking. In a meta-analysis conducted by Pinquart & Duberstein (2010) on social networks and cancer mortality, perceived social support, network size, and marital status were associated with decreases in relative risk for mortality. Still, there are mixed findings for whether perceived social support, network size, and marital status play a role in reducing mortality (De Boer, Ryckman, Pruyn, & Van den Borne, 1999). The lack of consensus among findings may be partially due to methodological inconsistencies and survey measures, which may be measuring the wrong construct.

The broad based model of potential pathways linking social support to physical health has two main pathways: (1) behavioral process and (2) psychological process, both influencing mortality and morbidity (Berkman et al., 2000; Cohen, 1988; Gore, 1981; Lin, 1986; Thoits, 1995; Umberson, 1987). Refer to Figure 1.

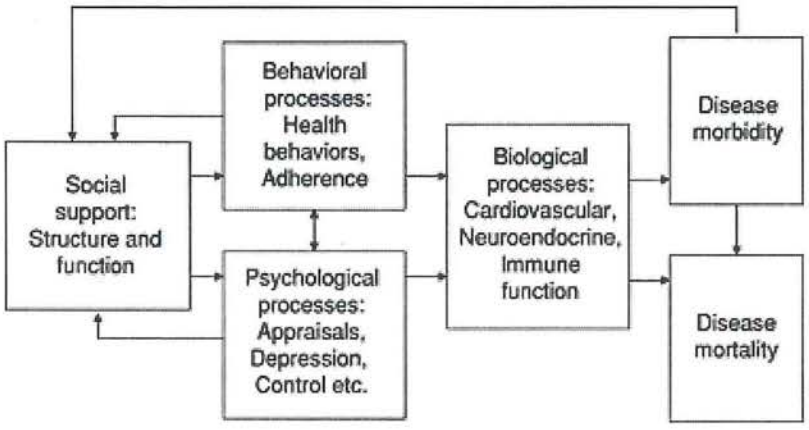
The focus of the first pathway is based on behavioral processes, including adherence to medical regimens and health behavior as constructed by social control and social identity theory (Lewis and Rook, 1999; Umberson, 1987). When patients experience positive social support, this may directly or indirectly facilitate health-promoting behavior. However, not all social support encourages healthy behavior, with some encouraging negative behavior (see reviews by Burg and Seeman, 1994; Wills and Yaeger, 2003).

The focus of the second pathway is based on psychological processes, which are associated with appraisals, emotions or moods, and feelings of control (Cohen, 1988; Gore, 1981; Lin, 1986). Evidence supports the relation between social support and these psychological processes. Currently, only mediating models are significant, lacking a direct relation between health outcome variables and psychological processes. Moreover, these

behavior and psychological pathways may have a reciprocal influence on the processes of social support, indicating that individuals who experience psychological distress may alter their perception of social support and contribute to a negative social interaction (Alferi et al., 2001; Coyne, 1976). This concept supports the Loneliness Model (Cacioppo & Hawkley, 2009; Cacioppo, Hawkley, Ernst et al., 2006), in that lonelier individuals who view their environment as more threatening, expect greater negative social interactions.

Additionally, there are two important components of the model which are the proposed links to and from disease morbidity and disease mortality. First, the link associated with disease morbidity signifies the importance of the potential role of social support and its part in the development of diseases. The second link is a feedback loop between disease morbidity and social support, indicating the various challenges diagnosed individuals face and how this impacts their social network (See Figure 1). According to Bolger et al. (1996) after diagnoses, individuals tend to reach out to close social networks as sources of support. Mixed results are associated with coping in overwhelming situations, with some individuals withdrawing from their social network to cope (Bolger et al., 1996), while other individuals see the overwhelming situation as a time to prosper in their personal relationships (Holahan & Moos, 1990).

Figure 1. Broad Based Model Indicating Potential Pathways Linking Social Support to Physical Health



Loneliness, Hypothalamic-Pituitary Adrenocortical Axis, and Immune Function

There are multiple biobehavioral pathways that affect brain-immune system outcomes. The major mediating physiological factors which affect clinical outcome are catecholamines, glucocorticoids, inflammation, angiogenesis, and cellular immune function (for reviews refer to Knight, Lyness, Sahler, Liesveld, & Moynihan, 2013). In the current paper, the focus is on glucocorticoids and cellular immune function.

The hypothalamic-pituitary-adrenocortical (HPA) axis mediates behavioral and physiological changes and adaptations through regulation of production and release of corticosteroid (Denver, 2009 & Schulkin, 2011). The HPA axis is activated by the hypothalamus, which secretes corticotropin-releasing hormone (CRH). CRH stimulates the anterior pituitary gland, releasing adrenocorticotropic hormone (ACTH). The distributing ACTH releases cortisol, which acts as the main regulator of the adrenal cortex.

The HPA axis acts as an important part of transforming physiology and behavior to promote energy, immune, and survival needs (Hawkley, 2012). In social species similar to humans, the HPA axis plays a role in physiological and behavioral mechanisms that sustains group structures. (Cacioppo & Hawkley, 2009; Cameron et al., 2009; Silk et al., 2009; Waynforth, 2011). As a result, social isolation in social species is a stressor which regularly leads to increased levels of cortisol (Cacioppo et al. 2011). Researchers have provided evidence that loneliness effects HPA functioning in older populations (Hawkley & Cacioppo, 2010; Luo, Hawkley, Waite, Cacioppo, 2012).

A type of a white blood cell, lymphocytes, has glucocorticoid receptors. The glucocorticoid receptors regulate a variety of functions of the lymphocytes. These functions include increasing lymphocyte production, recirculating lymphocytes through the blood and

lymph systems, and producing cytokines (small proteins that are important in cell signaling) (Ebrecht et al., 2000). Cole (2008) reported loneliness differences that are in sensitivity to glucocorticoid feedback focuses on the basic logic that exposure to glucocorticoids modifies the distribution of white blood cells in transmission. Mainly, an increase in cortisol production increases the circulating neutrophil percentages, decreasing circulating percentages of lymphocytes and monocytes. Thus, there is a greater ratio of neutrophils to monocytes and neutrophils to lymphocytes with higher levels of cortisol.

White blood cell (WBC) count is a clinical marker of inflammation and elevated WBC's are associated with mortality (Weiss, Segal, Sparrow, & Wager, 1995), cancer (Erlinger, Muntner, & Helzlsouer, 2004), cerebrovascular (Brown et al., 2004), and cardiovascular mortality (Margolis, et al., 2005). White blood cell count is an independent predictor for cardiovascular and cerebrovascular events (Brown et al., 2004; Wheeler, Mussolino, Gillum, & Danesh, 2004) and a negative prognostic factor in congenital heart disease patients (Brennan et al., 2003). A low lymphocyte count of eight percent or less of the WBC count and lymphocytes that have migrated into a tumor site (Alvaro-Naranjo et al., 2005; Schreck et al., 2009) are negative prognostic factors for survival in classical Hodgkin's Lymphoma (Hasenclever & Diehl, 1998).

Accordingly, oncology researchers are investigating lymphocyte/monocyte ratios (Porrata et al., 2012; Porrata et al., 2013), neutrophil/lymphocyte ratios (Chua, Charles, Baracos, & Clarke, 2011), and absolute monocyte counts at baseline of bone marrow transplants, day before chemotherapy, and at day 100 post bone marrow transplant to predict overall survival rate and progression rate in oncology patients. When the absolute neutrophil count to absolute lymphocyte count (N/L) ratio was greater at baseline there was an association with worse overall

survival in oncology patients (Chua et al., 2011; Halazun et al., 2008). Moreover, Azab (2008) determined that a larger N/L ratio is a predictor of greater mortality rates in breast cancer patients. In general, these results indicate that higher N/L ratios are associated with poorer survival rates in oncology populations. Additionally, elevated absolute neutrophil counts and absolute monocyte counts were associated with poor survival (Schmidt et al., 2005).

Loneliness and Hematology Oncology Population

In oncology populations, numerous psychosocial factors significantly affect the progress of cancer through biobehavioral pathways (Antoni et al., 2006; Cosanzo et al., 2011). Various researchers have identified several psychological processes as possible predictors of cancer progression, including mood, social support, stress, optimism, loneliness, and socioeconomic status (Cosanzo, 2011, Lutgendorf & Sood, 2011; McGregor & Antoni, 2009).

A common cancer group that is frequently treated with hematopoietic stem cell transplant (HSCT) and blood or bone marrow transplants (BMT) are hematological malignancies. Researchers are uncertain of the biobehavioral pathway, however previous research has indicated there is an association among psychosocial factors and HSCT outcomes (Hoodin et al., 2006). Minimal research has been pursued in psychoneuro-endocrinology or psychoneuro-immunology due to complexity in endocrine and immunological changes during HSCT, despite high psychological and immunological vulnerability (Costanzo et al., 2012).

In 2010, over 8000 allogeneic bone marrow transplants and more than 9000 autologous bone marrow transplants occurred in the United States (Center for International Blood and Marrow Transplant Research, 2012). The most common diseases are multiple myeloma followed by non-Hodgkin's lymphoma and acute myeloid leukemia.

Hematopoietic stem cell transplant and BMT entail an obliteration or near-complete ablation of native marrow with extremely high doses of chemotherapy, leaving patients with severely immunocompromised systems. There are two main types of transplants: (1) autologous - patient provides bone marrow or stem cells for self and (2) allogeneic - bone marrow or stem cells are provided from a matched donor. Even though direct investigation lacks, BMT treatment may encounter greater levels of distress than other cancer treatments (Knight et al., 2013). Depending on the type of transplant and institutional practice and complications, HSCT may involve extended periods of isolation, possibly leading to psychological disorders such as anxiety and depression (Sasaki et al., 2000).

There is inconsistent support on the relation between psychosocial variables, transplant related stressors and prior transplant psychological dysfunction (Hoodin et al., 2006). In a review of 19 research studies conducted by Hoodin et al. (2006), five of the studies resulted in no relation between negative emotion and survival; seven studies determined that individuals who experience greater negative emotion is associated with poorer survival rate, and five other research studies support positive emotion and pre-transplant optimism, hopefulness, and social support were positive predictors for longer survival.

Prior to a bone marrow transplant, conditioning or a preparative regimen occurs. Patients undergo several days of chemotherapy and/or radiation to destroy cancerous cells and bone marrow cells (American Cancer Society). This process destroys the immune system, leaving the patient vulnerable to infections. After conditioning, patients are in isolation between two to four weeks. Within the hospital, they are housed in private rooms with specialized filtered air, specialized diets, and restricted visitor access. Oncology staff, family, and friends must wash hands, wear protective gloves, gowns, and masks when entering a patient's room, to reduce the

spread and exposure to bacteria and viruses. The patient may experience perceived social isolation, psychological stress, and emotional stress during the isolation period and recovery. The recovery process is unstable with patients feeling great one day and ill and nauseas the next day. After the transplant, the patient's immune system is weak, with low white blood cell counts, lacking full immune protection against everyday viruses and bacteria. Contact with the general public is usually prohibited unless a mask is worn (American Cancer Society).

After a bone marrow transplant, there is a certain period during patient recovery where susceptibility to infections is greater. During the first six-weeks of BMT post-transplant, severe neutropenia and mucosal damage can occur, contributing to epidermis infections and harmful gastrointestinal organisms. Around two to three months post-transplant, humoral and cellular immunodeficiency remains a significant consideration (Knight et al., 2013). Cellular immunity fights against a virus with the assistance of T-helper lymphocytes (Th1 cells), producing specific cytokines that activate T-cytotoxic cells and natural killer cells. Humoral immunity responds against parasites and bacteria with the support of T-helper lymphocytes (Th2 cells), which produce different cytokines that specifically activate B cells and mast cells (Segerstrom, 2006). After three months, during the late recovery period, there is a reoccurring risk for viral reactivation, bacterial infection, and fungal pneumonia (Knight et al., 2013).

In addition to viruses and infections, there is still a significant risk for infections post-transplant. The biological consequences of psychosocial process are possibly important to the BMT/HSCT population because activation of biobehavioral pathways affect neuroendocrine function and contribute to the activity of viruses and regulation of immune response (Antoni et al., 2006). Stress hormones influence various viruses (Cohen et al., 1993; zur Hausen, 1991) which are significant causes of mortality and morbidity after BMT/HSCT (Boeckh et al., 2003).

More research is needed to investigate the relationship between neuroendocrine components of loneliness in BMT populations. The major goal of the current research is to investigate the neuroendocrine implications of loneliness in BMT patients throughout hospitalization and the recovery period. Another goal is to determine if loneliness experienced throughout hospitalization and loneliness in general are predictors of quality life at six-month post-transplant.

Hypothesis 1: Individuals who experience greater amounts of hospital loneliness will experience poorer overall quality of life at six-month post-transplant.

Hypothesis 2: Individuals who experience greater amounts of general loneliness will experience poorer overall quality of life at six-month post-transplant.

Hypothesis 3: When individuals experience more loneliness during hospitalization, their neutrophil to lymphocyte ratio will be greater 30 days after bone marrow transplant.

Hypothesis 4: Patients who experience greater amounts of loneliness during hospitalization will have a higher neutrophil to monocyte ratio 30 days after bone marrow transplant.

Method

The current study is part of a larger research study titled, "Complementary and Integrative Medicine Use and Disclosure in Blood and Marrow Transplant Patients." Two questionnaires were added to the original survey including the UCLA Loneliness Scale Version 3 and CARE measure. The main focus of this study is measures of loneliness and psychological and physical functioning outcomes.

Participants

One hundred and thirty one surveys were mailed to participants who endured a blood or bone marrow transplant at the Mayo Clinic of Jacksonville. Forty-one participants returned a completed survey and three participants completed the survey without a returned consent form, totaling 38 participants. The average age of the participants was 60 years old ($SD = 10.86$), ranging from 25 years of age to 75 years. Over half were female (55.3%, $n = 21$), Caucasian (84.2%, $n = 32$), married (81.6%, $n = 31$), and completed university or graduate level education (55.3%, $n = 21$). Close to 40% reported a household income greater than $60K ($n = 15$); most lived in their current housing arrangement for more than five years (92%, $n = 35$), and lived with spouse/partner (60.5%, $n = 23$) and/or children (23.7%, $n = 9$) at six-months post-transplant.

The majority of participants completed an autologous transplant (86.8%, $n = 33$) and were diagnosed with Myeloma (60.5% , $n = 23$). Half of the participants acquired at least one infection during transplant ($n = 19$). At six months post-transplant, over half of the participants reported their current health to be Good, Very Good, or Excellent (78.9%, $n = 30$), did not have other major medical issues (57.9%, $n = 22$), were not readmitted to the hospital (92.1%, $n = 35$), or did not have a recurrence of diagnosis (76.3%, $n = 29$). However, over half reported currently receiving some sort treatment (52.6%, $n = 20$).

Participants' average length of stay in hospital was 22 days ($SD = 6.67$) ranging from 14 days to 50 days, with the absolute neutrophil engraftment averaging 11.22 days ($SD = 2.00$), and platelet engraftment averaging 17.84 days ($SD = 3.16$). Loneliness reported during hospitalization ($M = 35.01$, $SD = 10.85$) was higher than general loneliness ($M = 32.50$, $SD = 10.61$), $t(37) = 2.12$, $p < .05$. Comparing bone marrow transplant participants' loneliness levels to the literature indicate somewhat lower levels of loneliness than college students and nurses (M

= 40.08, *SD* = 9.50; *M* = 40.14, *SD* = 9.52, respectively) and greater levels of loneliness than elderly population (*M* = 31.51, *SD* = 6.92) (Russell, 1996).

Average white blood cell (WBC) ratios at 30 days after the bone marrow transplant were obtained, including neutrophil to lymphocyte (N/L) and neutrophil to monocyte (N/M) ratios. They were calculated by gathering WBC data within three days before and after day 30 and averaging the levels for neutrophils, lymphocytes, and monocytes. Ratios were calculated using the averaged levels over the seven day range. On average, the neutrophil to lymphocyte (N/L) ratio at 30 days post-transplant was 4.24 (*SD* = 10.11), ranging from .16 to 63.83. The neutrophil to monocyte (N/M) ratio 30 days after bone marrow transplant was 4.18 (*SD* = 2.84), ranging from 1.30 to 15.61.

A N/L ratio greater than or equal to 3.1 is considered to be elevated, indicating a greater risk for mortality (Chua et al., 2011; Halazun et al., 2008) and loneliness is associated with a greater ratio of neutrophil to lymphocyte (Cole, 2008). Our N/L ratio was above the average.

McQuellon et al. (1997) reported at day 100 for bone marrow transplant patients, on average, overall quality of life was 112.4 (*SD* = 20.1) and social well-being (*M* = 23.5, *SD* = 3.8). The current participants overall quality of life (*M* = 107.95, *SD* = 20.77) and social well-being (*M* = 22.66, *SD* = 4.92) at six-month post-transplant were below the averaged quality of life and social well-being (McQuellon et al., 1997) at 100 days after BMT, indicating our sample is experiencing poorer overall quality of life and social well-being. Our sample reported slightly above average physical well-being (*M* = 21.11, *SD* = 5.40), emotional well-being (*M* = 18.00, *SD* = 5.07), functional-well-being (*M* = 17.95, *SD* = 6.97), and additional concerns about BMT (*M* = 28.23, *SD* = 5.53). In McQuellon et al. (1997) the average at day 100 of physical well-being was

20.8 (*SD* = 5.1), emotional well-being was 16.4 (*SD* = 3.2), functional-well-being was 17.4 (*SD* = 5.7), and additional concerns about BMT was 27.2 (*SD* = 5.7).

Procedure

Oncology/Hematology patients were identified through Mayo Clinic of Jacksonville Transplant Log. Each participant was over the age of 18 years and received a blood or bone marrow transplant. The survey packet was mailed +/- 30 days of the participants' six-month post-transplant date and included one survey, two inform consent forms, and one informational document. One to two weeks after the mailed survey packet, if the survey was not returned, a follow up call was conducted to remind patients about the research study. For study participation, a completed survey and one informed consent form was to be mailed to Mayo Clinic of Jacksonville. Medical information was obtained through PowerChart at the Mayo Clinic of Jacksonville, Florida.

UCLA Loneliness Scale Version 3

The UCLA Loneliness Scale Version 3 was used to assess general loneliness as well as the patients' loneliness during hospitalization. The original scale was modified with permission from the copyright holder, displaying the two set of 20 questions in two columns, parallel to one another. The modified UCLA Loneliness Scale asked participants to rate their feelings of loneliness during their hospital recovery from the transplant and how the participant generally feels (e.g. *"During your hospital recovery from the transplant... How often did you feel alone?"* and *"In general... How often do you feel alone?"*). Feelings of loneliness were rated on a Likert scale from 0 "*Never*" to 4 "*Always*". In addition, some items were reverse scored, so that higher scores on the UCLA Loneliness Scale indicate greater loneliness. For the general population, the average loneliness score is 40, ranging from 20 (little loneliness) to 80 (greatest loneliness).

Hospital loneliness and general loneliness were computed as two separate scores. The internal consistency for the UCLA Loneliness Scale Version 3 is very reliable with Cronbach's α ranging from .89 to .94 and a test-retest reliability of $r = .73$ (Russell, 1996). For the current study, reliability was strong for both loneliness scales (Hospital Loneliness Cronbach's α = .93; General Loneliness Cronbach's α = .94).

Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) Scale

The FACT-BMT is a validated, cancer specific quality of life instrument, measuring four well-being subscales (physical, social/family, emotional, and functional) and a bone marrow transplantation specific subscale (additional concerns). The questions were rated on a four-point Likert scale from 0 "*Not at all*" to 4 "*Very much*". Some questions were reversed scored, indicating a higher score denoting better functioning (ranging from 0 to 148). Instructions on handling missing data and calculating subscale and summary scores were followed according to the recommendations of McQuellon et al. (1997). Reliability for the FACT-BMT scale and subscales ranged from Cronbach's α's of 0.86 to 0.89, with the BMT subscale ranging from 0.54 to 0.63 (McQuellon et al., 1997).

For the current study, reliability was strong for the physical well-being (Cronbach's α = .87), social well-being (Cronbach's α = .87), and functional well-being (Cronbach's α = .86) subscales. Moderate reliability was found for the emotional well-being subscale (Cronbach's α = .67) and additional concerns about BMT subscale (Cronbach's α = .72).

Immunological Components

White blood cell (WBC) counts (i.e., absolute neutrophil count, absolute monocyte count, and absolute neutrophil count) were extracted from each patient's medical file through PowerChart at day 27 to day 33 after the bone marrow transplant. Two WBC ratios were

calculated: (1) ratio of neutrophil to lymphocyte was determined by dividing absolute neutrophil count into absolute lymphocyte count (N/L) and (2) ratio of neutrophil to monocyte was determined by dividing absolute neutrophil count into absolute monocyte count (N/M). WBC ratios have been associated as predictors of overall survivor in cancer populations and indicators of loneliness (Chua et al., 2011; Cole, 2008; Halazun et al., 2008; Porrata et al., 2013; Porrata et al., 2011).

Results

Bivariate Analysis

Several analyses were conducted regarding the association of hospital loneliness, general loneliness, and overall quality of life with categorical demographic and health variables. The results of these analyses are summarized in Table 1.

Hospital Loneliness

Married participants experienced less hospital loneliness than non-married participants, $F(1, 36) = 5.84, p < .05$. Hospital loneliness was not associated with race, age, education level, household income, sex, living arrangements, type of BMT, disease, current prescription use, nor currently receiving treatment. Moreover, it was not associated with physical well-being, emotional well-being, additional concerns about BMT, number of infections, managing transplant symptoms, length of hospital stay, neutrophil/lymphocyte ratio at day 30 after transplant, neutrophil/monocyte ratio at day 30 post-transplant, lymphocyte/monocyte ratio at day 30 post-transplant, days to absolute neutrophil count (ANC) engraftment nor days to platelet (PLT) engraftment, p's > .13 to .76. Participants who smoked in the past month reported greater amounts of loneliness than individuals who did not smoke, $F(1, 36) = 16.08, p < .0001$, although only three people reported smoking.

Hospital loneliness was significantly positively correlated with general loneliness [r (38), = .77, $p < .0001$] and problems managing symptoms over the past six months. Hospital loneliness was significantly negatively correlated with social well-being, functional well-being, and overall quality of life (refer to Table 2 for correlations). Hospital loneliness did not significantly predict physical well-being, emotional well-being, additional concerns about BMT, number of infections, managing transplant symptoms, length of hospital stay, days to ANC engraftment nor days to PLT engraftment, and therefore these criterion variables were not used in further multivariate analyses.

General Loneliness

Participants who are not married experienced greater amounts of loneliness overall than married participants, $F(1, 36) = 6.08$, $p < .013$. General loneliness was not associated with race, education level, age, household income, sex, living arrangements, type of BMT, disease, currently taking prescribed medication, currently receiving treatment, number of infections, length of hospital stay, days to ANC engraftment, nor days to PLT engraftment, p's > .06 to .98. Participants who smoked in the past month reported greater amounts of loneliness than individuals who did not smoke, $F(1, 36) = 8.77$, $p < .01$, although only three people reported smoking (See Table 1).

General loneliness was negatively correlated with social well-being, functional well-being, and overall quality of life (refer to Table 2 for correlations). General loneliness did not significantly predict physical well-being, emotional well-being, additional concerns about BMT, number of infections, length of hospital stay, days to ANC engraftment or days to PLT engraftment, and therefore was not used as criterion variables in multivariate analyses.

Overall Quality of Life

Participants who did not smoke in the past month reported greater overall quality of life than individuals who did smoke, $F(1, 36) = 6.64, p < .05$. Overall quality of life was negatively correlated with problems managing symptoms (refer to Table 2 for correlations). Overall quality of life was not associated with race, age, education level, marital status, household income, sex, living arrangements, type of BMT, disease, currently taking prescribed medication, currently receiving treatment, number of infections, length of hospital stay, days to ANC engraftment, nor days to PLT engraftment, p's > .18 to .99.

Infections, Symptoms, and Hospital Stay Bivariate Relations

Several analyses were conducted regarding the association of total infections, problems managing symptoms, and length of hospital stay with categorical demographic and health variables. The results of these analyses are summarized in Table 3.

Total Infections

Participants who were married developed more infections according to medical records than non-married participants $F(1, 36) = 10.50, p < .01$. Total number of infections were greater for participants who were living with a spouse/partner and or children $F(1, 36) = 8.31, p < .01$. Myeloma diagnosis was associated with fewer infections compared to other diseases $F(1, 36) = 5.96, p < .05$ (See Table 3).

Total number of infections was not associated with race, age, education level, household income, sex, nor type of BMT. Those patients currently taking prescribed medication, currently receiving treatment, or smoked in the past month did not have more infections, p's > .08 to .99. Moreover, total infections was not associated with hospital loneliness, general loneliness and overall quality of life, physical well-being, social well-being, emotional well-being, functional

well-being, or additional concerns about BMT, *p's* >.23 to .97. Therefore, the number of infections was not used as an outcome in further multivariate analyses with loneliness as a predictor.

Problem Managing Symptoms

Self-reported problems managing symptoms were not associated with any of the demographic or health variables, *p's* >.10 to .91. Problem managing symptoms was positively correlated with hospital loneliness [$r(38) = .38, p < .05$] and negatively correlated with overall quality of life [$r(38) = -.56, p < .0001$], physical well-being [$r(38) = -.56, p < .001$], functional well-being [$r(38) = -.44, p < .01$], and additional concerns about BMT [$r(38) = -.61, p < .0001$]. Additionally, problems managing symptoms were positively associated with neutrophil to lymphocyte ratio [$r(38) = .32, p < .05$], and neutrophil to monocyte ratio [$r(38) = 35, p < .05$].

Length of Hospital Stay

Length of hospital stay was not associated with any of the demographic or health variables. Also, length of stay was not associated with hospital loneliness, general loneliness and overall quality of life, physical well-being, social well-being, emotional well-being, functional well-being, or additional concerns about BMT, *p's* > .06 to .92. Therefore length of stay was not used in further analyses.

Engraftment Bivariate Relations

Several analyses were conducted regarding the association of absolute neutrophil count (ANC) engraftment and platelet engraftment with categorical demographic and health variables. The results of these analyses are summarized in Table 4.

Days to Engraftment

Days to ANC engraftment was not associated with any of the demographic or health variables, nor were there significant correlations between the variables, p's > .16 to .97. Days to PLT engraftment was not associated with any of the demographic or heath variables, nor were there significant correlations between the variables, p's > .17 to .98. Therefore days to ANC engraftment and PLT engraftment was not used for further analyses.

White Blood Cell Bivariate Relations

Several analyses were conducted regarding the association of neutrophil to lymphocyte ratio and neutrophil to monocyte ratio with categorical demographic and health variables. The results of these analyses are summarized in Table 5.

White Blood Cell Ratios Averaged Day 30 Post-Transplant

Averaged neutrophil to lymphocyte (N/L) ratio was positively associated with the averaged neutrophil to monocyte (N/M) ratio [$r(38) = .42, p < .01$] and problems managing current symptoms [$r(38) = .33, p < .05$]. Additionally, individuals who underwent an allogeneic bone marrow transplant had greater N/L ratio 30 days after the transplant than autologous bone marrow transplant patients, although there were only three allogeneic transplants (See Table 5).

Neutrophil/monocyte ratio was positively related to problems managing current symptoms [$r(38) = .34, p < .05$] and negatively associated with overall quality of life [$r(38) = -.53, p < .001$], physical well-being [$r(38) = -.41, p < .05$], emotional well-being [$r(38) = -.37, p < .05$], functional well-being [$r(38) = -.42, p < .01$], and additional concerns about bone marrow transplant [$r(38) = -.57, p < .0001$]. (Refer to Table 5).

Multivariate Analyses

Hospital Loneliness

Hierarchical linear regression analyses were used to investigate if hospital loneliness is a predictor of overall quality of life (QOL) and problems managing symptoms. Preliminary analyses were conducted to ensure no violation of assumptions of normality, linearity, multicollinearity and homoscedasticity for all analysis. A correlation matrix with variables included in analyses are summarized in Table 6. For all regression analyses, marital status was entered into Step 1 and hospital loneliness was entered into Step 2. For a summary of analysis refer to Table 7.

Hospital loneliness explained 14.4% of the variance in overall quality of life, after controlling for marital status, F change $(1, 35) = 6.08$, $p < .05$. The total variance explained by hospital loneliness and marital status was 17.0% ($p < .05$), with the full model significantly predictive of overall quality of life, F $(2, 35) = 3.59$, $p < .05$. Examination of Beta coefficients indicated that hospital loneliness was the only significant predictor of QOL in the model, with greater loneliness experienced during hospitalization associated with decreased QOL 6 months following transplant.

Hospital loneliness was independently associated with reported problems in managing symptoms ($\beta = .46$, $p < .01$) and accounted for over 17% ($\Delta R^2 = 17.8\%$) of the variance after controlling for marital status, F change $(1, 35) = 7.58$, $p < .01$. The total model accounted for 17.9% ($p < .01$) of variance and was significant in predicting symptom management issues, F $(2, 35) = 3.81$, $p < .05$. Elevated levels of loneliness experienced by patients during their hospital stay were associated with more difficulties in managing symptoms 6 months post-transplant.

Further analyses were conducted on overall quality of life to determine which subscales were significantly associated with hospital loneliness. Hierarchical linear regression was used to investigate if hospital loneliness was a predictor of physical well-being, social well-being, emotional well-being, functional well-being, and additional concerns about BMT, while controlling for marital status. For a summary of analysis refer to Table 7.

Hospital loneliness was found to be independently associated with functional well-being ($\beta = -.37, p < .05$) and explained 11.6% of the variance, after controlling for marital status, F change $(1, 35) = 4.65, p < .05$. The full model was not significantly predictive of functional well-being, $F\ (2, 35) = 2.59, p > .05$, and marital status only accounted for a very small and nonsignificant part of the variance (1.3%, p>.05).

Marital status accounted for 8.2% ($p > .05$) of the variances in social well-being, with hospital loneliness explaining an additional 16.2%, F change $(1, 35) = 7.49, p < .01$, (Total $R^2 =$ 24.4%, $p < .01$). The full model was predictive of social well-being, $F\ (2, 35) = 5.65, p < .01$, with only hospital loneliness statistically significant, ($\beta = -.43, p < .01$) in the final model. Greater levels of hospital loneliness predicted poorer social well-being at 6 months post-transplant.

Hospital loneliness was not found to be independently associated with physical well-being, emotional well-being nor additional concerns about BMT (p's > .06 to .44).

To investigate if hospital loneliness is a predictor of immunological functioning 30 days after BMT, utilizing white blood cell ratios, a hierarchical linear regression was used. Preliminary analyses were conducted to ensure no violation of assumptions of normality, linearity, multicollinearity and homoscedasticity for all analysis. A correlation matrix with variables included in analyses is summarized in Table 6. For all regression analyses, marital

status was entered into Step 1 and hospital loneliness was entered into Step 2. For a summary of analysis refer to Table 7.

Hospital loneliness was found to be independently associated with neutrophil/monocyte (N/M) ratio 30 days after the bone marrow transplant ($\beta = .36, p < .05$) and explained 11.0% of the variance after controlling for marital status, F change $(1, 35) = 4.31, p < .05$. The full model was not significantly predictive of the N/M ratio 30 days after transplant, $F(2, 35) = 2.17\ p > .05$, and marital status accounted for a minimal and nonsignificant part of the variance (0.00%, $p > .05$). Greater loneliness experienced during hospitalization was found to be independently associated with elevated ratio of neutrophil to monocyte ratio at 30 days after bone marrow transplant.

Hospital loneliness was not found to be independently associated with neutrophil to lymphocyte ratio at day 30 post-transplant ($p = .33$).

General Loneliness

Hierarchical linear regression was used to investigate if general loneliness is a predictor of overall QOL and problems managing symptoms. Preliminary analyses were conducted to ensure no violation of assumptions of normality, linearity, multicollinearity and homoscedasticity for all analysis. A correlation matrix with variables included in analyses is summarized in Table 6. For all regression analyses, marital status was entered into Step 1 and general loneliness was entered into Step 2. For a summary of analysis refer to Table 7.

General loneliness explained 22.3% of the variance in overall QOL, after controlling for marital status, F change $(1, 35) = 10.40, p < .01$. The total variance explained by general loneliness and marital status was 24.9%, with the full model significantly predictive of overall quality of life $F(2, 35) = 5.80, p < .01$. Examination of Beta coefficients indicated that general

loneliness was the only significant predictor of QOL in the model, with greater loneliness in general associated with poorer overall quality of life six-months following the transplant.

Further analyses were conducted on overall quality of life to determine which subscales were significantly associated with general loneliness. Hierarchical linear regression was used to investigate if general loneliness was a predictor of physical well-being, social well-being, emotional well-being, functional well-being, and additional concerns about BMT while controlling for marital status. For a summary of analysis refer to Table 7.

Marital status accounted for 8.2% ($p > .05$) of the variances in social well-being, with general loneliness explaining an additional 37.4%, F change (1, 35) = 24.07, $p < .001$ (Total R^2 = 45.6, $p < .0001$). The full model was predictive of social well-being, F (2, 35) = 14.68, $p < .001$, with only general loneliness statistically significant, ($\beta = -.67, p < .001$) in the final model. Greater levels of loneliness in general were associated with poorer social well-being at six months post-transplant.

General loneliness was found to be independently associated with emotional well-being ($\beta = -.38, p < .05$) and explained 12.0% of the variance, after controlling for marital status, F change (1, 35) = 4.76, $p < .05$. The full model was not significantly predictive of emotional well-being, F (2, 35) = 2.39, $p > .05$, and marital status only accounted for a very small and nonsignificant part of the variance (0.01%, $p > .05$).

General loneliness explained 15.5% of the variance in functional well-being, after controlling for marital status, F change (1, 35) = 6.51, $p < .05$. The total variance explained by general loneliness and marital status was 16.8%, with the full model significantly predictive of functional well-being F (2, 35) = 3.53, $p < .05$. Examination of Beta coefficients indicated that general loneliness was the only significant predictor of functional well-being in the model, with

greater loneliness in general associated with poorer functional well-being at six-months following the transplant.

General loneliness was not found to be independently associated with problems managing symptoms at six-months post-transplant, physical well-being nor additional concerns about BMT, *p's* > .12 to .33.

Discussion

Results indicated that whereas general loneliness was associated with quality of life (QOL) indicators such as social and emotional well-being, it is not significantly associated with problematic symptoms 6 months post-transplant nor immunological outcomes at day 30. Experiencing loneliness during the critical hospitalization period in which patients are rebuilding their immune system from a transplant is more predictive of continued problems managing symptoms six months after the transplant and poorer immunological functioning at 30 days post-transplant. Both hospital and general loneliness were found to be associated with QOL indicators of functional and social well-being.

Hypothesis one was predicted from previous research on hospital isolation and quality of life (Alpass & Neville, 2003; Berkman, 1995; Freyne et al., 2005; Piadala et al., 2013). Hypothesis one was supported in that experiencing greater degrees of loneliness during hospitalization was associated with poorer overall quality of life at six months post-transplant. Further analyses revealed that social well-being and functional well-being were the most impacted components of quality of life. In addition, patients who recalled greater amounts of hospital loneliness reported more problems managing symptoms six-months after a bone marrow transplant (BMT). These results imply that experiencing greater amounts of loneliness at the time of hospitalization can have long lasting effects with implications for every day functioning and

social well-being. This may lead to long-last side effects, creating stress, reducing immune functioning, and increasing health complications. Social isolation and loneliness are associated with poorer psychosocial well-being and adverse health outcomes (Alpass & Neville, 2003; Berkman, 1995; Freyne et al., 2005). According to Pidala et al. (2013) overall quality of life is associated with severity of graft-verse-host disease. Patients, who experience severe graft-verse-host disease and report more negative symptoms, on average, have poorer quality of life than patients experiencing a mild graft-verse-host disease. In addition, over time patients who reported more severe symptoms had poorer quality of life and reported less daily activities (Cohen et al., 2012). The current results further support previous research on the relationship between loneliness and poorer quality of life (Neitzert et al., 1998).

Researchers suggest that loneliness is associated with both poorer psychosocial outcomes and health outcomes (Ernst & Cacioppo, 1999). Hypothesis two was supported in that greater general loneliness was associated with poorer overall quality of life at six months post-transplant. Further analyses determined the quality of life components most impacted were social well-being, emotional well-being, and functional well-being. This indicates that individuals who tend to feel lonely do not feel as connected with friends and family members, which is associated with difficulty in performing everyday activities.

Loneliness is associated with depression, anxiety, and stress (Ernst & Cacioppo, 1999) which is related with poorer mental health and physical well-being (Cacioppo et al., 2000; Ernst & Cacioppo, 1999; Perkins, 1991), such as coping with an illness (McQuellen et al., 1997). Also, loneliness is associated with impaired cognitive functioning and cognitive decline over time (Gow et al., 2007; Tilvis et al., 2004; Wilson et al., 2007) which may result in difficulty completing everyday tasks such as working within or out of the home. Our results further support

current literature, indicating that lonelier individuals are associated with poorer emotional functioning, overall well-being, and negative health outcomes.

Moreover, these results support the Loneliness Model conceptualized by Cacioppo, Hawkley, Ernst et al. (2006). As bone marrow transplant patients experience more loneliness, they may perceive their environments as more threatening, expecting greater undesirable social interactions, and recalling more undesirable information six-month after the bone marrow transplant. These negative social expectations tend to provoke others to behave in a negative manner, confirming negative social expectations bone marrow transplant patients have preconceived. This relates back to the findings in those individuals who experience more loneliness in general is related to poorer social support and poorer emotional coping skills.

Another model the results support is the broad model based on potential pathways linking social support to physical health; see Figure 1 (Berkman et al., 2000; Cohen, 1988; Gore, 1981; Lin, 1986; Thoits, 1995; Umberson, 1987). The psychological process pathway indicates social support is linked to appraisals, emotions or moods, and feelings of control. Individuals who experience psychological distress, e.g. loneliness, may alter their perceptions of social support. This contributes to their misperceptions of a negative social interaction (Alferi, et al., 2001; Coyne, 1976). Loneliness and a poor social network are related to low quality of life, (Ekwall, Sivberg, Hallberg, 2004) poorer physical well-being, and poorer mental well-being (Ernst and Cacioppo, 1999; Gupta and Korte, 1994; Lui, 2007; Perkins, 1991). Loneliness impacts physical well-being and this has been linked to immune stress responses and worse cognition over time (Luanaigh & Lawlow, 2008). Our results provide further support of the broad based model. As an individual experiences loneliness, poor social support, and poor social well-being, these are associated with greater emotional distress and poorer everyday functioning. These outcomes may

negatively alter immunological functioning and biological function, in increasing disease morbidity and mortality.

Previous literature determines that oncology patients who have a stable social support system leads to better survival rates, higher quality of life, decreased depressive rates, less post-traumatic stress disorder symptoms, and decreased psychosocial morbidity (Booth-Jones, et al., 2002; Grassi, Indelli, Marzola, et al., 1996; Jacobsen, Sadler, Jenks Kettman, & Altmaier, 2008; Lloyd-Williams, & Friedman, 2001: Rodrigue, Pearman, & Moreb, 1991; Widows, Jacobsen, Booth-Jones, et al., 2005). Overall, stable and positive social support throughout the bone marrow transplant process has been linked to positive health outcomes (Frick, Ramm, Bumeder, et al., 2006; Lim & Zebrack, 2006; Rodrigue, Pearman, & Moreb, 1991). To further support this outcome, oncology patients who have relationships with problematic interactions were significantly associated with poor emotional and social function (Frick et al., 2006). Moreover, some patients feel safer expressing themselves in a support group setting instead of confiding to family members. This may occur due to family members being unable to understand the physical, social, and psychological impact of the transplant, changes in communication styles, changes in values, and patients' fatigue (Sherman, Cooke, & Grant, 2005). Relating back to the results, general loneliness is associated with poorer everyday functioning, such as work, which may lead to disruption of social support and social connectedness, and poorer emotional functioning.

Loneliness is considered a stressful experience (Hawkley 2003) and potentially a chronic stressor, which has negative effects on the immune and endocrine system functioning, increasing multiple health issues (Glaser & Kiecolt-Glaser, 2005) and the association with increased mortality risk (Luo, Hawkley, Waite, & Cacioppo, 2012). As stated in the Evolutionary Model,

(Cacioppo & Hawkely, 2003) when an individual perceives their surrounding environment as threatening, survival mechanisms activate, intensifying threats from all relationships. This negative social interaction may hinder physiological functioning, interfering with immune function. A bone marrow transplant is an isolating and stressful experience which may be associated with poorer immunological functioning.

To further support the current literature, we were interested in determining if there is a relationship between loneliness experienced during hospitalization and the neutrophil to monocyte ratio 30 days after a bone marrow transplant. Hypothesis four was supported in that experiencing loneliness during hospitalization was associated with a higher neutrophil to monocyte ratio 30 days after a bone marrow transplant. These results imply that loneliness experienced at the time of hospitalization is associated with immunological functioning, which may hinder the recovery process and complicating BMT health issues.

Loneliness has adverse consequences for health and mortality, indicating that greater feelings of loneliness are associated with increased mortality risk (Luo, Hawkley, Waite, & Cacioppo, 2012). In support of hypothesis four, when individuals experience frequent loneliness, as little as one day per week, cortisol is stimulated, increasing circulating concentrations of neutrophils and reduces the concentrations of lymphocytes and monocytes (Cole, 2008). Furthermore, an individual who experiences subjective social isolation is an independent risk factor for variations in leukocyte sensitivity in glucocorticoid regulation (Cole et al., 2007). Fauci, Dale, & Balow (1976) recognized that the longest effects of glucocorticoids involve the regulation of leukocyte subset composition within circulating blood. When levels of glucocorticoids are high, they increase the circulating number of neutrophils and decrease the circulating numbers of lymphocytes and monocytes (Dale, Fauci et al. 1975; Dhabhar, Miller et

al. 1996; Fauci, Dale et al. 1976; Miller, Spencer et al. 1994). Overall, our findings are consistent with previous literature and models. Individuals who experience greater amounts of loneliness during hospitalization have a higher count of neutrophil and a decreased count of monocytes. However, our findings did not support previous literature, in that individuals who experience more hospital loneliness have a greater neutrophil to lymphocyte count 30 days after hospitalization.

In relating back to the broad based model of potential pathways linking social support to physical health (Berkman et al., 2000; Cohen, 1988; Gore, 1981; Lin, 1986; Thoits, 1995; Umberson, 1987), both hospital loneliness and general loneliness are related to quality of life. Specifically, functional well-being, social well-being, and emotional well-being are related to loneliness. Loneliness during hospitalization is associated with immunological functioning 30 days after a bone marrow transplant. This relationship is associated with poorer immunological functioning which may be connected to disease morbidity and mortality. However, the direction of the relationship cannot be determined due to the correlational design of this study.

Hypotheses three was not supported. Specifically, loneliness experienced during the hospital stay was not associated with a greater neutrophil to lymphocyte ratio at 30 days post-transplant. These results may be due to the small sample size which is associated with low levels of power for the analyses. However, the results were trending in a positive direction, displaying more loneliness potentially being associated with greater neutrophil to lymphocyte ratio.

Jaremka et al. (2012) determined that lonelier breast cancer survivors are associated with increased pain, depression, and fatigue symptom cluster after treatment, in comparison with non-lonely breast cancer survivors. Immune dysregulation has been determined as a potential link and connecting health and loneliness, indicating the importance between loneliness and pain,

depression and fatigue. Loneliness, pain, depression, and fatigue are associated with serious illness or disease, placing individuals at risk for poor health and premature mortality (Becker et al., 1997; Hardy & Studenski, 2008; Schulz et al., 2000). Moreover, individuals who reported greater loneliness at baseline had higher baseline and stress induced inflammation compared to those who felt as if they were more socially connected (Hackett 2012; Jaremka inpress). Our results are consistent with previous research, with loneliness during hospitalization being associated with more problems managing symptoms, poorer social well-being, and functional well-being at six months post-transplant. Experiencing loneliness may hinder the recovery process, both physiological and psychological. Minimal research has been conducted on bone marrow transplant patients and investigating loneliness during the hospital stay and the relationship between psychosocial outcomes and physiological outcomes.

Researchers need to determine the bidirectional relation between the types of psychological change that is required to translate into a biological or physiological change. This may lead to determining which psychological interventions are most effective to benefit health outcome rates in bone marrow transplant patients. A review by Antoni (2012) emphasized the importance of cognitive, behavioral, and social factors as tools of intervention to assist adaptation to all stages of cancer survivorship. Four relevant interventions have been investigated: (1) exercise; (2) mind-body; (3) cognitive behavioral stress management; and (4) psychopharmacologic agents. These interventions as well as others have advantageous effects on neuroendocrine and immune function and psychological functioning. Yet, interventions on bone marrow transplant populations are limited and lack intensive research due to the complications of the transplant (Antoni, 2012).

Loneliness is related to stress, anxiety, depression, impaired cognitive functioning and cognitive decline (Ernst & Cacioppo, 1999; Gow et al., 2007; Tilvis et al., 2004; Wilson et al., 2007). By increasing positive social support and reducing feelings of loneliness this may improve emotional well-being in regards to the bone marrow transplant process. In having positive social support and feelings of social connection bone marrow transplant patients psychological and physiological functioning may improve over time. This will result in a reduction of negative health outcomes and better at managing symptoms after a bone marrow transplant. Moreover, in reducing loneliness and increasing social connection patients, may experience both a better bone marrow transplant procedure and quality of life which may lead to a greater overall survival rate.

Limitations

The study was retrospectively completed, asking participants to recall six-months post-transplant about their hospital experience. Due to the transplant being an arduous procedure and requiring numerous hospital visits from the time of bone marrow transplant discharge to completion of survey, recall of hospital loneliness may be inaccurate or misconstrued (Sternberg & Sternberg, 2012). General loneliness was identified as how lonely the participants were feeling overall. This may be interpreted as a trait since loneliness in general can vary depending on an individual's psychosocial well-being. Quality of life was considered an outcome measure. This indicated that quality of life may change throughout the bone marrow transplant recovery process. Another limitation was the correlational study design. With marital status being significantly correlated with hospital loneliness and general loneliness, we controlled for marital status in analyses to assess independent relationships. A third limitation was small sample size; (i.e. 38 participants) a greater response rate would increase the statistical power and results.

Another limitation was the lack of participant responses and the attrition rate within the bone marrow transplant population. The survey was completed by around 33% of the bone marrow transplant patients at Mayo Clinic in Jacksonville, Florida. A greater response rate to the survey may have occurred if participants completed the survey at the six-month post-transplant follow-up hospital visit.

Future research

Since stress, loneliness, and cortisol modify immune function (Glaser & Kiecolt-Glaser, 2005) bone marrow transplant patients may be at risk for immune dysregulation pre-transplant, during transplant, and post-transplant. Future research should investigate and determine the relationship between loneliness and immunological functioning in bone marrow transplant patients. When a relationship exists, it may be due to the complicated immune system or psychological distress experienced prior to a bone marrow transplant, during a bone marrow transplant, and/or after a bone marrow transplant. Additional work should examine other psychosocial factors, such as types of social support, quality of social support, and quality of social connection during a bone marrow transplant. Moreover, the psychology factors that alter immunological outcomes at admission of bone marrow transplant, during transplant, and after transplant need further investigation.

Another future research aim should investigate pre-transplant loneliness and perception of overall outcome. A longitudinal design may better predict overall survival and outcome rates for bone marrow transplant patients. To predict overall survival and outcome rates, data should be collected prior to a bone marrow transplant, day of transplant, time of discharge from bone marrow transplant, 30 day post-transplant, day 100 after the transplant, six-months after the transplant, and one year post-transplant. Another suggestion would be to investigate the

caregiver's perception of the BMT patients' hospital and general loneliness and perceived stress. Future research may provide a glimpse into how loneliness affects immunological functioning in determining overall quality of life, social well-being, emotional well-being, functional well-being, and physical well-being, post-bone marrow transplant.

Conclusion

Increased overall loneliness is associated with poorer overall quality of life in multiple dimensions, in addition experiencing loneliness during hospitalization is associated with symptom functioning at six-month post-transplant. Moreover, loneliness during hospitalization is associated with a greater neutrophil to monocyte ratio 30 days after a bone marrow transplant, indicating there is a relationship between hospital loneliness and immunological functioning during the recovery process. Investigation still remains as to whether loneliness and other psychosocial factors mediate immunological functioning and how this relation affects overall quality of life after a bone marrow transplant. There are multiple biobehavioral pathways that are affected by psychosocial factors. This mediating relation needs to be further investigated, producing valid and reliable results similar to other oncology populations. Replicablility of both positive and negative psychological outcome factors need to be established, which may lead to a further understanding of type of social connection and social support, thereby reducing loneliness. These research propositions are critical to improving pre-transplant process, reducing fears and anxiety recovery from transplant, and life after transplant, contributing to the advancement of psycho-oncology research.

Table 1: Average Hospital Loneliness, General Loneliness, and Overall Quality of Life by Demographic and Health Variables

		Hospital Loneliness		General Loneliness		Overall QOL	
Variables	*n*	*M*	SD	*M*	SD	*M*	SD
Racial Background							
Caucasian	32	33.95	10.44	31.13	9.40	107.54	20.72
Non-Caucasian	6	40.67	12.226	39.83	14.44	110.17	22.87
Education							
HS/Partial College	17	35.82	13.75	30.29	11.68	109.50	19.89
University/Graduate Level	21	34.36	8.09	35.24	9.37	106.70	21.85
Marital Status							
Married	31	33.11	9.928	30.52	8.87	109.52	20.92
Not Married	7	43.43*	11.49	41.29*	13.83	101.01	20.01
Household Income							
< $60K	15	35.80	12.63	33.67	11.39	110.26	21.77
> $60K	15	35.97	9.480	32.60	10.99	108.01	20.87
Prefer not to answer	8	31.75	10.39	30.13	9.22	103.51	20.64
Sex							
Male	17	35.62	10.34	34.09	12.53	105.89	23.95
Female	21	34.52	11.47	31.09	8.84	109.62	18.22
Current Living Arrangements							
Living with spouse and/or children	32	33.86	10.64	31.09	9.31	109.00	20.79
Not Living with spouse and/or children	6	41.17	10.74	40.00	14.68	102.35	21.57
BMT							
Autologous	33	34.08	10.91	32.42	10.84	109.39	20.22
Allogeneic	3	44.33	11.02	33.68	13.87	99.72	7.02
Disease							
Myeloma	23	36.33	11.41	34.48	11.27	107.95	21.17
Other	15	33.00	9.98	29.47	9.05	107.95	20.86
Prescription Medication Regularly							
Yes	36	35.26	4.950	32.58	10.90	106.87	20.80
No	2	30.50	11.070	31.00	2.83	127.50	3.54
Currently Receiving Treatment							
Yes	20	34.48	10.04	30.60	8.27	108.26	20.85
No	17	36.35	11.89	35.29	12.68	108.17	20.83
Smoked in the Past Month							
Yes	3	55.33***	7.64	48.33**	10.02	80.33*	15.53
No	35	33.27	9.23	31.14	9.63	110.32	19.54

Note: HS/Partial College = high school, partial college, and/or technical college completed; < $60K = less than $60,000; > $60K = greater than $60,000; BMT = bone marrow transplant. $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .0001$

Table 2: Correlation Matrix between Variables

Variables	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.
1. Hospital Loneliness	1.00											
2. General Loneliness	.77***	1.00										
3. Marital Status	.37*	.39*	1.00									
4. Problem Managing Symptoms	.38*	.26	-.03	1.00								
5. Overall QOL	-.41**	-.49***	-.16	-.56***	1.00							
6. SWB	-.48**	-.68***	-.29	-.25	.58***	1.00						
7. PWB	-.16	-.19	-.09	-.56***	.69***	.28	1.00					
8. EWB	-.28	-.31	.03	-.19	.65***	.22	.15	1.00				
9. FWB	-.36*	-.41*	-.12	-.44**	.87***	.37*	.44**	.59***	1.00			
10. AC	-.26	-.29	-.13	-.61***	.87**	.36*	.69***	.43**	.68***	1.00		
11. N/L Ratio	.19	-.14	-.09	.36*	-.10	.10	.09	-.05	-.23	-.22	1.00	
12. N/M Ratio	.30	.16	-.02	.34*	-.53***	-.15	-.41*	-.37*	-.37*	-.42**	.57***	1.00

Note: Days until ANC Engraftment = days until absolute neutrophil count engraftment; days until platelet count engraftment; LOS = length of stay in the hospital; Overall QOL = overall quality of life; PWB = physical well-being; SWB = social/family well-being; EWB = emotional well-being; FWB = functional well-being; AC = additional concerns about bone marrow transplant; N/L Ratio = neutrophil/lymphocyte ratio at day 30; N/M Ratio = neutrophil/monocyte ratio at day 30. $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .0001$.

Table 3: Average Number of Infections, Problem Managing Symptoms, and Length of Stay by Demographic and Health Variables

		Number of Infections		Problem Managing Symptoms		Length of Stay	
Variables	*n*	*M*	SD	*M*	SD	*M*	SD
Racial Background							
Caucasian	32	1.25	1.00	12.66	6.73	22.81	6.87
Non-Caucasian	6	.33	.82	9.67	5.96	17.67	3.20
Education							
HS/Partial College	17	.94	1.03	11.23	6.64	23.48	8.14
University/Graduate	21	1.05	1.2	12.95	6.68	20.18	3.71
Marital Status							
Married	31	1.23**	.99	12.29	6.99	22.06	4.70
Not Married	7	.00**	.00	11.71	5.12	21.71	12.82
Household Income							
< $60K	15	.80	1.01	11.07	5.91	19.93	3.58
> $60K	15	1.20	1.01	13.40	6.88	21.80	5.62
Prefer not to answer	8	1.00	1.07	12.00	7.86	26.25	10.81
Sex							
Male	17	1.06	1.03	11.47	6.95	20.47	5.20
Female	21	.95	1.02	12.76	6.47	23.24	7.56
Current Living Arrangements							
Living with spouse and/or children	32	1.19*	.99	12.41	6.91	22.09	4.62
Not Living with spouse and/or children	6	.00*	.00	11.00	5.21	21.50	14.03
BMT							
Autologous	33	.97	1.01	11.67	6.54	21.67	7.03
Allogeneic	3	.67	1.15	19.67	3.51	23.67	4.04
Disease							
Myeloma	23	.70*	.97	12.87	5.96	20.35	5.54
Other	15	1.47*	.92	11.13	7.63	24.53	7.62
Prescription Medication Regularly							
Yes	36	1.00	1.41	12.58	6.58	22.03	6.36
No	2	31.00	1.01	5.00	.00	21.05	6.78
Currently Receiving Treatment							
Yes	20	1.10	1.20	11.85	5.98	23.50	8.11
No	17	.94	1.29	12.24	7.55	20.50	4.12
Smoked in the Past Month							
Yes	3	.67	1.15	17.67	2.89	21.00	4.36
No	35	1.03	1.01	11.71	6.67	22.09	6.87

Note: HS/Partial College = high school, partial college, and/or technical college completed; < $60K = less than $60,000; > $60K = greater than $60,000; BMT = bone marrow transplant. $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .0001$

Table 4: Days to ANC Engraftment and Days to PLT Engraftment by Demographic and Health Variables

		Days to ANC Engraftment			Days to PLT Engraftment	
Variables	*n*	*M*	SD	*n*	*M*	SD
Racial Background						
Caucasian	31	11.19	2.136	31	17.65	3.251
Non-Caucasian	5	11.40	.894	6	18.83	2.639
Education						
HS/Partial College	15	11.33	2.193	16	17.24	3.360
University/Graduate	21	11.14	1.905	21	17.24	3.360
Marital Status						
Married	30	11.20	2.156	31	17.81	3.410
Not Married	6	11.33	1.033	6	18.00	1.414
Household Income						
< $60K	13	11.85	1.676	14	18.64	2.951
> $60K	15	11.27	2.219	15	17.27	3.807
Prefer not to answer	8	10.13	1.808	8	17.50	2.000
Sex						
Male	17	11.71	2.339	16	17.95	3.025
Female	19	10.79	1.584	21	17.69	3.420
RC_Living Arrangements						
Living with spouse and/or children	31	11.26	2.144	32	17.84	3.361
Not Living with spouse and/or children	5	11.00	.707	5	17.80	1.483
BMT						
Autologous	31	11.10	2.12	32	18.03	2.978
Allogeneic	3	12.00	1.00	3	18.33	1.155
Disease						
Myeloma	21	10.90	2.26	22	17.82	1.842
Other	15	11.67	1.54	15	17.87	4.533
Prescription Medication Regularly						
Yes	34	11.21	2.06	35	17.77	3.237
No	2	11.50	.71	2	19.00	.000
Currently Receiving Treatment						
Yes	19	11.26	2.16	20	17.20	3.665
No	16	11.19	1.94	16	18.69	2.358
Smoked in the Past Month						
Yes	3	11.67	1.16	2	16.50	3.536
No	33	11.18	2.07	35	17.91	3.175

Note: Days to ANC Engraftment = days to absolute neutrophil count engraftment; Days to PLT Engraftment = days to platelet engraftment; HS/Partial College = high school, partial college, and/or technical college completed; < $60K = less than $60,000; > $60K = greater than $60,000; BMT = bone marrow transplant. Two participants never went below ANC of 500 and were not used in the analysis. One participant never went below platelet count of 20,000 and was not used in the analysis. $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .0001$

Table 5: Average Neutrophil/Lymphocyte (N/L) Ratio and Neutrophil/Monocyte (N/M) Ratio at Day 30 Post-Transplant by Demographic and Health Variables

		N/L Ratio		N/M Ratio	
Variables	*n*	*M*	SD	*M*	SD
Racial Background					
Caucasian	32	4.75	10.95	4.16	3.05
Non-Caucasian	6	1.55	1.21	4.30	1.29
Education					
HS/Partial College	17	2.30	1.26	3.24	3.43
University/Graduate Level	21	5.81	13.49	4.95	1.48
Marital Status					
Married	31	4.68	11.16	4.21	3.10
Not Married	7	2.31	1.24	4.06	1.19
Household Income					
< $60K	15	2.53	1.21	3.65	1.23
> $60K	15	6.11	15.97	4.03	2.70
Prefer not to answer	8	3.01	2.59	5.47	4.73
Sex					
Male	17	2.52	2.10	3.84	2.46
Female	21	5.63	13.45	4.46	3.14
Current Living Arrangements					
Living with spouse and/or children	32	4.67	10.98	4.18	3.06
Not Living with spouse and/or children	6	1.93	.79	4.20	1.24
BMT					
Autologous	33	2.34	1.57	3.84	2.60
Allogeneic	3	23.69***	34.78	5.45	3.10
Disease					
Myeloma	23	2.57	2.57	4.21	3.02
Other	15	6.80	6.80	4.14	2.64
Prescription Medication Regularly					
Yes	36	4.33	10.38	4.23	2.89
No	2	2.65	1.10	3.31	1.65
Currently Receiving Treatment					
Yes	20	2.87	2.44	4.60	3.46
No	17	5.90	14.96	3.53	1.81
Smoked in the Past Month					
Yes	3	3.86	1.49	5.26	1.75
No	35	4.27	10.54	4.09	2.91

Note: HS/Partial College = high school, partial college, and/or technical college completed; < $60K = less than $60,000; > $60K = greater than $60,000; BMT = bone marrow transplant. *$p < .05$, **$p < .01$; ***$p < .0001$

Table 6: Correlation between Hospital Loneliness, General Loneliness, and Criterion Variables in Hierarchical Linear Regression

	Loneliness			
	Hospital		General	
Criterion Variable	*r*(*n*)	*p*	*r*(*n*)	*p*
Age	-.17(38)	.31	-.11(38)	.49
Overall QOL	-.41(38)*	.01	-.50(38)**	.00
PWB	-.16(38)	.35	-.19(38)	.26
SWB	-.48(38)**	.00	-.68(38)***	.00
EWB	-.28(38)	.09	-.31(38)	.06
FWB	-.36(38)*	.03	-.41(38)	.01
AC	-.26(38)	.11	-.29(38)	.08
Total Number of Infections	-.20(38)	.23	-.20(38)	.23
Managing Symptoms	.38(38)*	.02	.26(38)	.12
Days to ANC	.04(38)	.84	.03(38)	.88
Days to PLT	-.08(38)	.66	.09(38)	.58
N/L Ratio	.12(38)	.48	-.15(38)	.39
N/M Ratio	.30(38)	.07	.16(38)	.33

Note: Overall QOL = overall quality of life; PWB = physical well-being; SWB = social/family well-being; EWB = emotional well-being; FWB = functional well-being; AC = additional concerns about bone marrow transplant; Managing symptoms = problem managing symptoms, Days to ANC Engraftment = days to absolute neutrophil count engraftment; Days to PLT Engraftment = days to platelet engraftment. N/L Ratio = neutrophil/lymphocyte averaged ratio at day 30; N/M Ratio = neutrophil/monocyte averaged ratio at day 30. $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .0001$.

Table 7: Hierarchical Linear Regression of Hospital and General loneliness predicting Quality of life and Hospital Variables

	Loneliness					
	Hospital			General		
Criterion Variables	B	SEB	β	B	SEB	β
Overall QOL	-.783	.318	-.409*	-1.008	.313	-.515**
PWB	-.069	.090	-.139	-.090	.092	-.178
SWB	-.197	.072	-.433**	-.309	.063	-.667***
EWB	-.155	.081	-.331	-.180	.083	-.377*
FWB	-.236	.109	-.367*	-.282	.110	-.429*
AC	-.127	.090	-.249	-.146	.092	-.280
Total Number of Infections	-.002	.015	-.024	-.001	.015	-.011
Managing Symptoms	.278	.101	.455**	.203	.110	.325
N/L Ratio	.166	.167	.178	---	---	---
N/M Ratio	.093	.049	.357*	---	---	---

Note: Overall QOL = overall quality of life; PWB = physical well-being; SWB = social/family well-being; EWB = emotional well-being; FWB = functional well-being; AC = additional concerns about bone marrow transplant; Managing symptoms = problem managing symptoms; N/L Ratio = neutrophil/lymphocyte ratio at day 30; N/M Ratio = neutrophil/monocyte ratio at day 30. Controlled for Marital status. $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .0001$.

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Name and Clinic Number

IRB # 10-003464 00
Consent form approved **June 21, 2011:**
This consent valid through **June 12, 2012:**

1. General Information About This Research Study

Study Title: Complementary and Integrative Medicine Use and Disclosure in Blood and Marrow Transplant Patients

Name of Principal Investigator on this Study: Dr. Steven Ames and Colleagues

A. Study Eligibility and Purpose

You are being asked to take part in this research study because you have received a blood or marrow transplant. We would like to better understand the frequency and reasons for use of complementary and alternative medicine in blood and marrow transplant patients. Additionally, we would like to better understand whether patients tell their healthcare providers about their use of complementary and alternative medicine. We are also interested in learning about how patients recovery may be effected by loneliness and their satisfaction with the doctors who provided their care during the transplant process.

As you read this form describing the study, ask any questions you have. Take your time to decide. Feel free to discuss the study with your family, friends, and healthcare provider before you decide. If you decide to participate, you may stop participating at any time during the study. You may decide not to participate. If so, none of your current benefits or normal health care will be affected in any way. When you feel comfortable that all your questions have been answered, and you wish to take part in this study, sign this form in order to begin your participation. If you are agreeing for someone else, you need to sign this form. Your signature means you have been told about the study and what the risks are. Your signature on this form also means that you want yourself, or your child/relative/principal/ward to take part in this study.

B. Number of Participants

The plan is to have 50 people take part in this study at Mayo Clinic.

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2. What Will Happen To You While You Are In This Research Study?

If you agree to be in the study, you will be asked to complete four questionnaires one time. The first questionnaire is named the Complementary and Alternative Medicine Survey and asks about your use of complementary and alternative medicines. The second questionnaire is named the Functional Assessment of Cancer Therapy-Blood and Marrow Transplantation and asks about your quality of life. The third questionnaire is named UCLA Loneliness Scale and asks about feelings of loneliness. The fourth questionnaire is named Consultation and Relational Empathy Measure and asks about the your satisfaction with your relationship with the doctors who cared for you while in the hospital for your transplant. It is estimated that these questionnaires will take approximately 15 minutes to complete. You will have the option of completing the questionnaire at home at your convenience, and mailing it in a self-addressed, postage-paid envelope.

3. How Long Will You Be in This Research Study?

You will be in the study until you complete the four questionnaires.

4. Why You Might Want To Take Part In This Research Study

This study will not make your health better. It is for the benefit of research.

5. What Are the Risks Of This Research Study?

Some questions you will be asked to answer in the study questionnaire(s) may make you feel uncomfortable. You may choose not to answer any questions that make you feel uncomfortable.

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Risk summary
The risks of this research study are minimal, which means that we do not believe that they will be any different than what you would experience at a routine clinical visit or during your daily life.

6. What Other Choices Do You Have If You Don't Take Part In This Research Study?

This study is only being done to gather information. You may choose not to take part in this study.

7. Are There Reasons You Might Leave This Research Study Early?

Taking part in this research study is voluntary. You may decide to stop at any time. You should tell the researcher if you decide to stop and you will be advised whether any additional tests may need to be done for your safety.

In addition, the researchers, The American Cancer Society, or Mayo may stop you from taking part in this study at any time:

- if it is in your best clinical interest.
- if you do not follow the study procedures.
- if the study is stopped.

8. Will You Need To Pay For Any Of The Tests And Procedures?

You will not need to pay for tests and procedures which are done just for this research study. These tests and procedures are:

- Completing a questionnaire about your use of complementary and alternative medicines.

However, you and/or your health plan will need to pay for all other tests and procedures that you would normally have as part of your regular clinical care.

If you have study related questions regarding billing, insurance or reimbursement, stop by or call: The receptionist at the Registration Desk at the first floor, main lobby of the Davis Building

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9. Will You Be Paid For Participating In This Research Study?

You will not be paid for taking part in this study.

10. What Happens If You Are Injured Or Ill Because You Were In This Research Study?

If you have side effects from taking part in this study, you need to report them to the researcher and your regular physician, and you will be treated as needed. Mayo will give medical services for treatment for any bad side effects from taking part in this study. Such services will be free if not covered by a health plan or insurance. No additional money will be offered.

11. What Are Your Rights If You Are In This Research Study?

Taking part in this research study will not change your rights and benefits. Taking part in this research study does not give you any special privileges. If you decide to not participate in this study, or stop in the middle of the study, no benefits are taken away from you. You do not have to be in this research study to receive or continue to receive medical care from Mayo Clinic.

You will be told of important new findings or any changes in the study or procedures that may affect you or your willingness to continue in the study.

12. What About Your Privacy?

Authorization To Use And Disclose Protected Health Information
Your privacy is important to us, and we want to protect it as much as possible. By signing this form, you authorize Mayo Clinic and the investigators to use and disclose any information created or collected in the course of your participation in this research protocol. This information might be in different places, including your original medical record, but we will only disclose information that is related to this research protocol for the purposes listed below.

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This information will be given out for the proper monitoring of the study, checking the accuracy of study data, analyzing the study data, and other purposes necessary for the proper conduct and reporting of this study. If some of the information is reported in published medical journals or scientific discussions, it will be done in a way that does not directly identify you.

This information may be given to other researchers in this study, including those at other institutions, or private, state or federal government parties or regulatory authorities in the USA and other countries responsible for overseeing this research. These may include the Food and Drug Administration, the Office for Human Research Protections, or other offices within the Department of Health and Human Services, and the Mayo Clinic Office for Human Research Protections or other Mayo groups involved in protecting research subjects.

If this information is given out to anyone outside of Mayo, the information may no longer be protected by federal privacy regulations and may be given out by the person or entity that receives the information. However, Mayo will take steps to help other parties understand the need to keep this information confidential.

This authorization lasts until the end of the study.

The study does not end until all data has been collected, checked (or audited) and analyzed. Sometimes this can be years after your study visits have ended. For example, this could happen if the results of the study are filed with a regulatory agency like the Food and Drug Administration.

13. What Will Happen to Your Samples?

No biological samples will be collected as part of this research study.

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14. Who Can Answer Your Questions?

You can call ...	At ...	If you have questions or concerns about ...
Principal Investigator: Steven C. Ames, Ph.D.	Phone:	Questions about the study tests and procedures Research-related injuries or emergencies Any research-related concerns or complaints
Mayo Clinic IRB Research Subject Advocate	Phone: Toll-Free:	Rights of a research subject Use of Protected Health Information or any research-related concerns or complaints
Research Billing	Florida:	Billing / Insurance Questions

15. Summary and Enrollment Signatures

You have been asked to take part in a research study, at Mayo Clinic. The information about this study has been provided to you to inform you about this study.

- I have read the whole consent form, and all of my questions have been answered to my satisfaction.
- I am satisfied that I have been given enough information about the purpose, methods, risks, and possible benefits of the study to decide if I want to join.
- I know that joining the study is voluntary and I agree to join the study.
- I know that I can call the investigator and research staff at any time with any questions or to tell them about side effects.
- I know that I may withdraw from the study at any time.
- I will be given a copy of this completed form.

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Please sign and date to show that you have read all of the above guidelines. Please do not sign unless you have read this entire consent form. If you do not want to sign, you don't have to, but if you don't you cannot participate in this research study.

(Date / Time)	(Printed Name of Participant)	(Clinic Number)

(Signature of Participant)

(Date / Time)	(Printed Name of Individual Obtaining or in Receipt of Consent)

(Signature of Individual Obtaining or in Receipt of Consent)

Mayo Clinic: Office for Human Research Protection
Contact Letter Template

Protocol Title: Complementary and Integrative Medicine Use and Disclosure in Blood and Marrow Transplant Patients

IRB #: 10-003464
Principal Investigator: Dr. Steven Ames and Colleagues

(Date}

{Name}
{Street Address}
{City, State Zip}

RE: *{first name} {last name}*
MC#: *{mc #}*

Dear *{Mr., Ms, or Mrs. }*

You are being asked to take part in this research study because you have received a blood or marrow transplant. We would like to better understand the frequency and reasons for use of complementary and alternative medicine in blood and marrow transplant patients. Additionally, we would like to better understand whether patients tell their healthcare providers about their use of complementary and alternative medicine.

If you agree to be in the study, you will be asked to complete four questionnaires one time. The first questionnaire is named the Complementary and Alternative Medicine Survey and asks about your use of complementary and alternative medicines. The second questionnaire is named the Functional Assessment of Cancer Therapy-Blood and Marrow Transplantation and asks about your quality of life. The third questionnaire is named UCLA Loneliness Scale and asks about feelings of loneliness. The fourth questionnaire is named Consultation and Relational Empathy Measure and asks about your satisfaction with your relationship with the doctors who cared for you while in the hospital for your transplant. It is estimated that these questionnaires will take approximately 15 minutes to complete. We have enclosed the questionnaires to complete. If you would like to, you may fill it out and return in the enclosed stamped envelope.

The risks of this research study are minimal, which means that we do not believe that they will be any different than what you would experience at a routine clinical visit or during your daily life. However, it is possible that some questions you will be asked to answer in the study questionnaires may make you feel uncomfortable. You may choose not to answer any questions that make you feel uncomfortable.

This study will not make your health better. It is for the benefit of research and may aid us in helping people in the future by better understanding the frequency and reasons for use of complementary and alternative medicine in blood and marrow transplant patients.

Please understand your participation is voluntary and you have the right to withdraw your consent or discontinue participation at any time without penalty. Specifically, your current or future medical care at the Mayo Clinic will not be jeopardized if you choose not to participate.

If you decide to participate, please read and sign the consent form and return with the questionnaires. An extra copy is included for your records.

If you have any questions about this research study you can contact me at
If you have any concerns, complaints, or general questions about research or your rights as a participant, please contact the Mayo Institutional Review Board (IRB) to speak to someone independent of the research team at or toll free at

If you prefer to complete the survey over the phone, or if you do not wish to participate, please indicate on the next page and return this letter since it will make a follow-up telephone call unnecessary. Thank you very much for your time and consideration.

Sincerely,

Steven C. Ames, Ph.D., ABPP
Principal Investigator

RE: *{first name}{ last name}*
MC#: *{mc #}*

☐ I would prefer to complete the survey over the phone. I am enclosing the **Authorization to Use and Disclose Protected Health Information form** only. Please call me.

Your name: _____
Telephone number: (___)___-____
Today's date: __/__/__
Best time to call: ☐ Morning ☐ Afternoon ☐ Evening
Best day(s) to call:_____

☐ I am **not** willing to participate in this research study.

Today's Date: ☐☐ / ☐☐ / ☐☐☐☐
Month Day Year

Birthdate: ☐☐ / ☐☐ / ☐☐☐☐
Month Day Year

1. **What is your medical diagnosis, for which you received a BMT?**

_____

2. **Are you receiving any treatment currently?** ○ No ○ Yes

_____

3. **Have you had a recurrence since your BMT?**

○ No ○ Yes Date: ☐☐ / ☐☐ / ☐☐☐☐
Month Day Year

4. **Do you have any other major medical issues at this time?**

○ No ○ Yes

_____

_____

_____

_____

5. **Would you say that your current health is (check one):**

○ Excellent ○ Very good ○ Good ○ Fair ○ Poor

6. **Ethnic group (check one):**

○ Hispanic/Spanish/Latino ○ Not Hispanic/Spanish/Latino

7. **Racial Background (check one):**

○ American Indian or Alaskan Native ○ Native Hawaiian/Pacific Islander

○ Asian ○ White

○ Black or African American ○ More than one race (specify): _____

8. **Marital Status (check one):**

○ Never married ○ Divorced

○ Currently married ○ Widowed

○ Separated

---

9. What is your current living arrangement (check one)

- ◯ Live alone
- ◯ Live with spouse/partner
- ◯ Live with spouse/partner and children
- ◯ Live with children (no spouse/partner)
- ◯ Live with roommate who is not partner
- ◯ Live with parents
- ◯ Other (specify): _____

10. Number of children living at home (enter 0 if none): ☐☐☐

11. How long in current living arrangement (check one):

- ◯ Less than 1 month
- ◯ One to 6 months
- ◯ Seven months to less than 2 years
- ◯ Two to 5 years
- ◯ More than 5 years

12. Level of school completed (check one):

- ◯ Less than 7th grade
- ◯ Junior High School (7th, 8th, & 9th grade)
- ◯ Partial High School (10th or 11th grade)
- ◯ High School graduate
- ◯ Partial college or specialized training
- ◯ College or university graduate
- ◯ Graduate professional training (graduate degree)

13. Current employment situation (check the one box that applies the most):

- ◯ Full time at job
- ◯ Part time at job
- ◯ On leave with pay
- ◯ On leave without pay
- ◯ Disabled
- ◯ Seeking work
- ◯ Retired
- ◯ Homemaker
- ◯ Student

14. Which category best describes your usual occupation? If you are not currently employed, which category best describes your LAST job? (check one):

- ◯ Professional (e.g., teachers/professors, nurses, lawyers, physicians, & engineers)
- ◯ Manager/Administrator (e.g., sales managers)
- ◯ Clerical (e.g., secretaries, clerks, or mail carriers)
- ◯ Sales (e.g., sales persons, agents, or brokers)
- ◯ Service (e.g., police, cooks, waiters, or hairdressers)
- ◯ Skilled Crafts, Repairer (e.g., carpenters)
- ◯ Equipment or Vehicle Operator (e.g., truck drivers)
- ◯ Laborer (e.g., maintenance or factory workers)
- ◯ Farmer (e.g., owners, managers, operators, or tenants)
- ◯ Member of the military
- ◯ Homemaker (with no job outside the home)
- ◯ Other (please describe) _____

15. Which category best describes your spouse's usual occupation? If your spouse is not currently employed, which category best describes his/her LAST job? (check one box):

- ◯ Professional (e.g., teachers/professors, nurses, lawyers, physicians, & engineers)
- ◯ Manager/Administrator (e.g., sales managers)
- ◯ Clerical (e.g., secretaries, clerks, or mail carriers)
- ◯ Sales (e.g., sales persons, agents, or brokers)
- ◯ Service (e.g., police, cooks, waiters, or hairdressers)
- ◯ Skilled Crafts, Repairer (e.g., carpenters)
- ◯ Equipment or Vehicle Operator (e.g., truck drivers)
- ◯ Laborer (e.g., maintenance or factory workers)
- ◯ Farmer (e.g., owners, managers, operators, or tenants)
- ◯ Member of the military
- ◯ Homemaker (with no job outside the home)
- ◯ Other (please describe) _____

16. What is <u>your</u> approximate annual gross income? (check one box)
(Remember all information you provide will remain completely confidential)

◯ Less than $10,000 ◯ $40,000 - $59,999 ◯ Prefer not to answer
◯ $10,000 - $19,999 ◯ $60,000 - $100,000
◯ $20,000 - $39,999 ◯ Greater than $100,000

17. Approximate annual gross income for your <u>household</u>: (check one box)
(Remember all information you provide will remain completely confidential)

◯ Less than $10,000 ◯ $40,000 - $59,999 ◯ Prefer not to answer
◯ $10,000 - $19,999 ◯ $60,000 - $100,000
◯ $20,000 - $39,999 ◯ Greater than $100,000

18. Do you take prescription medication regularly? ◯ No ◯ Yes

If YES, what do you take?

Drug	Dose	Since	Reason

39655

19. Have you had any trouble managing the following symptoms over the past 6 months?

	No Problem	Just a little	Moderate	Some difficulty	As bad as it can be
1. Pain	○	○	○	○	○
2. Nausea	○	○	○	○	○
3. Fatigue	○	○	○	○	○
4. Sleep	○	○	○	○	○
5. Anxiety	○	○	○	○	○
6. Emotional Distress	○	○	○	○	○
7. Mobility	○	○	○	○	○
8. Infections	○	○	○	○	○
9. Skin Problems	○	○	○	○	○
10. Sexual Function	○	○	○	○	○
11. Overall quality of life	○	○	○	○	○
12. Other:_____	○	○	○	○	○

20. During your lifetime, have you smoked at least 100 cigarettes (5 packs or more)?

○ No ○ Yes

IF YES:

a). How many cigarettes do/did you typically smoke each day?

☐☐☐ (# cigarettes)

b). Have you smoked in the past month?

○ Yes approximately ☐☐☐ cigarettes per day

○ No , I quit about ☐☐ years **OR** ☐☐ months ago

c). How many years in total have you smoked, or if you have quit, how many years did you smoke?

☐☐ (Number of years)

21. **Have you had any alcoholic drinks in the past month?**

○ No ○ Yes

IF YES:

a). Which of the following best describes the number of alcoholic drinks you had in the past month? (check one) (Note: One drink equals: one 12 oz. can of beer, one 6 oz. glass of wine, or one 1 oz. shot of hard liquor)

○ 1-3 times a month ○ 1 time a day

○ 1-3 times a week ○ 2 times a day

○ 4-6 times a week ○ 3 or more times a day

22. **Have you used (illicit) non-prescription drugs (for example, marijuana, cocaine) in the past month?**

○ No ○ Yes

IF YES:

a). What drug(s) did you use?

_____

b). How often did you use the drug(s) in the past month? (check one)

○ 1-3 times a month ○ 1 time a day

○ 1-3 times a week ○ 2 times a day

○ 4-6 times a week ○ 3 or more times a day

FACT-BMT (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.

	PHYSICAL WELL-BEING	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

	SOCIAL/FAMILY WELL-BEING	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	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-BMT (Version 4)

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

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GB1	I feel sad	0	1	2	3	4
GB2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GB3	I am losing hope in the fight against my illness	0	1	2	3	4
GB4	I feel nervous	0	1	2	3	4
GB5	I worry about dying	0	1	2	3	4
GB6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	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-BMT (Version 4)

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

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
BMT1	I am concerned about keeping my job (include work at home)	0	1	2	3	4
BMT2	I feel distant from other people	0	1	2	3	4
BMT3	I worry that the transplant will not work	0	1	2	3	4
BMT4	The effects of treatment are worse than I had imagined	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
C3	I like the appearance of my body	0	1	2	3	4
BMT5	I am able to get around by myself	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
BMT7	I have concerns about my ability to have children	0	1	2	3	4
BMT8	I have confidence in my nurse(s)	0	1	2	3	4
BMT9	I regret having the bone marrow transplant	0	1	2	3	4
BMT10	I can remember things	0	1	2	3	4
B4	I am able to concentrate	0	1	2	3	4
BMT11	I have frequent colds/infections	0	1	2	3	4
BMT12	My eyesight is blurry	0	1	2	3	4
BMT13	I am bothered by a change in the way food tastes	0	1	2	3	4
BMT14	I have tremors	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
BMT15	I am bothered by skin problems (e.g., rash, itching)	0	1	2	3	4
BMT16	I have trouble with my bowels	0	1	2	3	4
BMT17	My illness is a personal hardship for my close family members	0	1	2	3	4
BMT18	The cost of my treatment is a burden on me or my family	0	1	2	3	4

UCLA Loneliness Scale (Version 3)

Instructions: The following statements describe how people sometimes feel. Please complete the first column for how you felt **during your recovery from the transplant while in the hospital** and the second column for how you **generally** feel. **For each statement**, please indicate how often you felt the way described by writing a number (1,2,3, or 4) in the space provided. If you feel that the question is not applicable to your experience, please write N/A.

Please write one of the following numbers on each line corresponding to how often you feel the way described in the question: NEVER 1 RARELY 2 SOMETIMES 3 ALWAYS 4

#	**During your hospital recovery from the Transplant...**	**In general....**
1.)	____ How often did you feel that you were in tune with the people around you?	____ How often do you feel that you are in tune with the people around you?
2.)	____ How often did you feel that you lacked companionship?	____ How often do you feel that you lack companionship?
3.)	____ How often did you feel that there was no one you could turn to?	____ How often do you feel that there is no one you can turn to?
4.)	____ During your recovery from the transplant in the hospital, how often did you feel alone?	____ How often do you feel alone?
5.)	____ How often did you feel part of a group of friends?	____ How often do you feel part of a group of friends?
6.)	____ How often did you feel that you had a lot in common with the people around you?	____ How often do you feel that you have a lot in common with the people around you?
7.)	____ How often during your inpatient recovery period did you feel that you were no longer close to anyone?	____ How often do you feel that you are no longer close to anyone?
8.)	____ How often did you feel that your interests and ideas were not shared by those around you?	____ How often do you feel that your interests and ideas are not shared by those around you?

Please write one of the following numbers on each line corresponding to how often you feel the way described in the question: NEVER 1 RARELY 2 SOMETIMES 3 ALWAYS 4

#	During your hospital recovery from the Transplant...	In general....
9.)	____ While being an inpatient during your transplant recovery, how often did you feel outgoing and friendly?	____ How often do you feel outgoing and friendly?
10.)	____ How often did you feel close to people?	____ How often do you feel close to people?
11.)	____ How often did you feel left out?	____ How often do you feel left out
12.)	____ How often did you feel that your relationships with others were not meaningful?	____ How often do you feel that your relationships with others are not meaningful?
13.)	____ How often did you feel that no one really knew you well?	____ How often do you feel that no one really knows you well?
14.)	____ During your recovery from the transplant while in the hospital, how often did you feel isolated from others?	____ How often do you feel isolated from others?
15.)	____ How often did you feel you could find companionship when you wanted it?	____ How often do you feel you can find companionship when you want it?
16.)	____ How often did you feel that there were people who really understood you?	____ How often do you feel that there are people who really understand you?
17.)	____ How often did you feel shy?	____ How often do you feel shy?
18.)	____ While recovering from your transplant as an inpatient, how often did you feel that people were around you but not with you?	____ How often do you feel that people are around you but not with you?
19.)	____ How often did you feel that there were people you could talk to?	____ How often do you feel that there are people you can talk to?
20.)	____ How often did you feel that there were people you could turn to?	____ How often do you feel that there are people you can turn to?

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MEGAN CURTIS

EDUCATION

Master of Arts in General Psychology, August 2014
University of North Florida, Jacksonville, Florida

Bachelor of Arts in Psychology, April, 2011
University of North Florida, Jacksonville, Florida

EMPLOYMENT

Distant Learning Assistant, Center for Instructional Research Technology, September, 2012 – Present
University of North Florida, Jacksonville, Florida

- Blackboard technical support for instructors and faculty
- Develop course content for distant learning courses
- Aid Instructional Designers with creation of online course
- Assist professors with ParScore, Respondus, and StudyMate

RESEARCH

CRISP Intern, Research Assistant, January 2013 – Present
Mayo Clinic, Jacksonville, Florida
Topic: Oncology/Hematology and Liver Transplants

- Extract patient's medical information
- Organize and Manage large data sets in Excel and SPSS
- Conduct statistical analysis

Research Assistant, January 2013 – April 2013
University of North Florida, Jacksonville, Florida
Topic: Civic Minded Learning

- Analyzed, recoded, and rescaled over 300 variables
- Conducted statistical analysis
- Presented statistical findings to supervisors

TEACHING

Instructor of Record, Research Methods Lab, Fall 2013 and Spring 2014
University of North Florida, Jacksonville, Florida

- Developed and instructed weekly lectures utilizing SPSS
- Created syllabus and Maintained weekly office hours
- Graded through Blackboard

Graduate Teaching Assistant for Experimental Cognitive Psychology, Spring 2013 and Summer 2013
University of North Florida, Jacksonville, Florida

- Assisted in preparation of course syllabus
- Created rubrics and assisted in grading assignments
- Conducted lecture and review sessions

CONFERENCES

Curtis, M., Lange, L., & Ames, S. *Due to a bone marrow transplant, is loneliness from hospital isolation a predictor of health outcome?* Poster presentation at Southeastern Psychological Association (SEPA) on March 6, 2014

Curtis, M., Balfour, L., Lange, L., & Ames, S. *Loneliness During Bone Marrow Transplant Hospitalization and Recovery.* Poster presentation at Society of Southeastern Social Psychologists (SSSP) on November 9, 2013

CERTIFICATION and TRAINING

Blackboard Learn Certification
Advanced Teaching & Learning Online
University of North Florida, September 2013

Human Subjects Protection Training Program
Protecting Human Research Participants
Mayo Clinic, December 2012

Integrity and Compliance Education Program
Mayo Clinic, December 2012

Collaborative Institutional Training Initiative (CITI)
Human Research: Social and Behavioral Research Investigator
University of North Florida, March 2013

STUDY ABROAD

Cuzco, Peru
June 2010 – July 2010

- Visited Colegio Pukllansunchis, an inclusive educational system
- Observed school psychological evaluations
- Assisted with student's school assignments
- Interacted and engaged with Peruvian Primary and Secondary students
- Visited Manos Unidas, school serving disabled children from VPK through Secondary