Cognitive Dysfunction in non-Hodgkin's Lymphoma Patients Treated with Front-Line Chemotherapy

by

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Abstract

Despite the research to date, the characteristics and impact of cognitive dysfunction (CD) in cancer patients following chemotherapy is still not well understood. It is estimated approximately 20% of patients will manifest measurable cognitive deficits on neuropsychological testing post-chemotherapy. Given the increasing incidence of cancer, significant numbers of patients could potentially experience CD. Declines in cognitive function may compromise the ability to adhere to treatment requirements, to make informed treatment-related decisions, and to manage work-related activities.

The purpose of this study was to document the frequency of occurrence, severity and duration of CD in non-Hodgkin's lymphoma patients receiving front-line chemotherapy, and to determine what factors (if any) are correlated with CD in these patients.

A quantitative, descriptive, prospective, observational design was utilized: Data were collected at five time points (pre-treatment, mid-treatment, and at one, six and 12 months post-treatment). Both subjective (patient perception) (FACT-Cog) and objective (neuropsychological) testing measures (CogState) were used. An estimate of premorbid intelligence was obtained using the NAART35. Information on possible confounding variables (eg. depression, anxiety, stress, fatigue, quality of life, hemoglobin) was collected via standardized questionnaires at each timepoint. Total time for completion of the testing at each timepoint was approximately 1 hour.

A total of 100 subjects (65 males, 35 females) between 26 to 88 years of age were enrolled into this study between November 2010 and February 2014. The analyses of the results for this dissertation include the first 3 assessment time-points, and were completed

using group data: Within-subject statistics will be obtained at the completion of all follow-up assessments. A subset of subjects reported worsening of perceived cognitive function over time as they progressed through their course of chemotherapy, with up to 41% of subjects reporting deterioration in quality of life as a consequence of cognitive impairment and with a worse quality of life associated with more subjective cognitive complaints. Perceived cognitive impairment was associated with higher levels of fatigue, depression, anxiety and stress. Doxorubicin-containing chemotherapy was associated with an increase in concerns regarding cognitive abilities, compared to non-doxorubicin containing regimens. Modest to moderate correlations were seen between the objective tasks measuring visual attention, working memory, attention and executive function and perceived (subjective) cognitive concerns.

To my knowledge, this is the first longitudinal, prospective study investigating cognitive function in lymphoma patients receiving standard dose chemotherapy. As such, the results of the study will add important information to the literature in this group of patients.

Preface

This thesis is an original work by Joanne Dorothea Hewitt. The research project, of which this thesis is a part, received research ethics approval from the Alberta Cancer Research Ethics Committee, Project Name "Cognitive Dysfunction in non-Hodgkin's Lymphoma Patients Treated with Front-Line Chemotherapy", No. 25438 , August 25, 2010 and reciprocal approval from the University of Alberta Research Ethics Board, September 24, 2010.

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Chapter 1: Statement of the Problem

Many of the side effects of cancer chemotherapy are generally well documented, with established interventions that are relatively effective at controlling or relieving the symptoms. Other side effects such as chemotherapy-induced cognitive dysfunction (often called "chemo brain"), are less well understood and thus the development of interventions for these has been limited. Although the incidence and severity of cognitive dysfunction (CD) in patients with cancer is generally not well documented in the literature (Bender, Paraska, Sereika, Ryan, & Berga, 2001), studies have reported 16% to 75% of cancer patients receiving chemotherapy experience some degree of CD (Coyne & Leslie, 2004; Paraska & Bender, 2003; Staat & Segatore, 2005; Tchen et al., 2003; Wieneke & Dienst, 1995). "Cognitive deficits are generally mild to moderate in severity and associated with both standard-dose and high-dose adjuvant chemotherapy, although higher doses are often linked with more severe and persistent impairment. Cognitive deficits are frequently noted during chemotherapy and also have been observed up to 10 years following treatment" (O'Shaughnessy, 2003, p. 17).

Some authors have proposed associations between CD and factors other than chemotherapy including fatigue, depression, anxiety, stress, postmenopausal status, age, educational status, pain, analgesics and other concomitant medications (Bender et al., 2001; Staat & Segatore, 2005), but the causal pathways are far from clear. At the time of conceptualization and design of the current research proposal, no studies were identified on the literature review which had systematically compared the relationships among these

factors and CD in individuals receiving chemotherapy and individuals not receiving chemotherapy.

Relatively few studies of CD in individuals receiving chemotherapy have been published since 1980 (Anderson-Hanley, Sherman, Riggs, Agocha & Compas, 2003; Bender et al., 2001; Jansen, Miaskowski, Dodd, & Dowling, 2005; Olin, 2001). The majority of these studies have been in breast cancer patients undergoing adjuvant chemotherapy; however, a few studies have reported cognitive impairment in patients with other types of cancer including hematologic malignancies and testicular cancer (Staat & Segatore, 2005).

CD may manifest as changes in various cognitive domains including short-term memory, concentration, attention span, language skills, organizational skills, information processing time and/or reaction time, and executive functions such as hindsight, foresight and judgment (Coyne & Leslie, 2004; Olin, 2001; O'Shaughnessy, 2003; Staat & Segatore, 2005). These changes may impair decision-making and impinge on the patient's ability to fulfill family, career and community responsibilities (Bender et al., 2001; Dietrich, Monje, Wefel & Meyers, 2008). "The clinical features of chemo brain … can become a serious detriment to multitasking, create stress, and weaken performance when patients are challenged by high-level cognitive demands, including acquiring new skills" (Staat & Segatore, 2005. p. 713), thus potentially adversely affecting the patient's daily functioning and quality of life. Additionally, as a consequence of the limited longitudinal research conducted to date as well as variation in study results, the duration and reversibility of CD following completion of chemotherapy has not yet been established

(Ahles et al., 2002; Schagen et al., 2002; van Dam et al., 1998; Wefel, Collins, & Kayl, 2008).

The limited research literature available about CD leaves oncology health care professionals without the knowledge base required to confidently discuss this potential toxicity with their patients or to manage it effectively. Some health care professionals may not be aware of the potential impact that even subtle cognitive symptoms can have on social and vocational functioning (Meyers, 2000). Health care professionals working with cancer patients experiencing CD have attempted to use interventions developed for other populations, such as minor head injury or neurological illness; however, there is limited empirical information in the adult oncology population on the effectiveness of these approaches (Grober, 2002; Locke, Cerhan, & Malec, 2008; McAllister et al., 2004). Furthermore, given the specialized nature of the health care system, oncology health care professionals may not be familiar with these potential interventions since they were originally designed for and tested in other patient populations.

Patient Perceptions of Cognitive Dysfunction

In my clinical experience many cancer patients complain of CD. Some of the descriptions they give include: “not being able to think clearly”, “feeling like being in a fog”, “forgetful”, and “unable to concentrate”. They often ask the same questions over and over again, requiring repeated teaching as they are unable to remember information they have previously been taught.

A common finding of the studies conducted in cognitive impairment is that there does not appear to be a relationship between patients’ perceptions of cognitive changes

and objective neuropsychological test results (Cimprich, 1992; Cull et al., 1996; Schagen et al, 1999; van Dam et al., 1998). Patients who complained of memory problems, either in interviews or on the cognitive function portion of quality of life questionnaires, were not necessarily those who showed evidence of dysfunction on testing (van Dam et al., 1998). Possible reasons for this discrepancy could be related to lack of sensitivity in the test measures used, as the tests may have little relationship to the skills required for everyday functioning (Cull et al., 1996; Rugo & Ahles, 2003; Schagen et al., 1999; van Dam et al., 1998); that is, they lack ecological validity (American Academy of Neurology, 1996; Tannock, Ahles, Ganz, & van Dam, 2004). On the other hand, a relationship was found between self reported memory and concentration problems and psychological/emotional distress (anxiety and depression) (Cull et al., 1996; van Dam et al., 1998), whereas the objective test performance was not correlated with cognitive complaints (Schagen et al., 1999). It is estimated that 20% - 25% of cancer patients experience unrecognized and untreated long-term depression (Lee et al., 2006). Cognitive changes related to anxiety include slowed mental processing, blocked thoughts and complaints of memory deficits, with depression affecting executive function, processing speed, attention, and memory (Kurita, Lundorff, de Mattos Pimenta, & Sjøgren, 2009). Therefore, in order to ensure that cognitive changes related to depression and/or anxiety are not inadvertently attributed to the effects of chemotherapy, measures to assess for the presence of these symptoms must be included in trials investigating chemotherapy related cognitive function.

High functioning individuals may be more aware of cognitive deficits, resulting in greater difficulties coping with subtle cognitive changes (Kolb & Whishaw, 2009; Staat &

Segatore, 2005). A number of factors can influence how disruptive cognitive dysfunction is to an individual:

a) characteristics of the injury or insult (e.g., structure vs. neurochemical, location, severity);
b) characteristics of the individual (e.g., pre-morbid cognitive functioning, age, presence of co-morbid conditions);
c) characteristics of the environment (e.g., demands of job, degree of social support, presence of rehabilitation opportunities) (Castellon & Gantz, 2001, p. 624).

Quality of Life Issues/Impact of Cognitive Dysfunction

The relationship between quality of life issues and cognitive dysfunction is complex. Whereas minimal and subtle cognitive changes may have profound effects on daily, social, occupational and educational functioning for one individual, another individual with more pronounced cognitive deficits may experience little effect on quality of life (Ahles & Saykin, 2001; Garofalo & Baum, 2001; Olin, 2001). "The functional impact of a specific impairment depends upon the individual's ability to compensate for it – a process that generally requires the ability to recognize the problem, marshal resources, anticipate when the problem will occur and monitor the success of the compensatory strategy" (Nail, 2006, p.48). Thus, the effect on each individual will vary depending on pre-morbid cognitive ability, age, current responsibilities, the perceived effect the changes have had on daily activities, quality of life, and other factors specific to the individual (see Appendix A: Potential Contributory Factors to Cognitive Function & Quality of Life). Because there are individual differences in normal attentional capacity, it is important to

assess patients for changes in concentration and attention abilities compared to their baseline or pre-morbid level of functioning, rather than comparing to a population norm (Cimprich, 1995; O'Shaughnessy, 2003).

Purpose of Study

The purpose of this study was to document the frequency of occurrence, severity and duration of cognitive impairment in non-Hodgkin's lymphoma patients receiving front-line chemotherapy at the Cross Cancer Institute, and to determine what factors (if any) were correlated with cognitive deficits experienced by these patients.

Research questions. The research questions were:

1. What are the manifestations of cognitive dysfunction/impairment over time in non-Hodgkin's lymphoma patients receiving front-line chemotherapy at the Cross Cancer Institute?

2. What factors predict cognitive dysfunction/impairment experienced by non-Hodgkin's lymphoma patients receiving front-line chemotherapy at the Cross Cancer Institute?

3. Is there a correlation between objective (neuropsychological) and subjective (perceived) cognitive assessments in non-Hodgkin's lymphoma patients receiving front-line chemotherapy at the Cross Cancer Institute?

4. Is there a correlation between cognitive dysfunction/impairment and quality of life in non-Hodgkin's lymphoma patients receiving front-line chemotherapy at the Cross Cancer Institute?

Definition of Terms

1. *Non-Hodgkin's lymphoma (NHL) patients* – adult patients with a histological diagnosis of non-Hodgkin's lymphoma.

2. *Front-line or first-line chemotherapy* – the initial chemotherapy regimen patients receive for treatment of their NHL.

3. *Cognitive dysfunction/cognitive impairment* - any alteration in intellectual functioning or specific deficits in cognitive abilities. One or more of the cognitive domains (e.g., attention and concentration, information processing speed, memory (verbal and visuospatial), learning, language, executive function, visuospatial skill, and psychomotor ability) may be affected.

4. *Subjective cognitive deficits* – patient self-reported alterations and/or deficits in cognitive abilities, as measured by a standardized questionnaire.

5. O*bjective cognitive deficits* - alterations and/or deficits in cognitive abilities, as measured by standardized neuropsychological instruments.

6. *Quality of life* – patient self-reported assessment of "the extent to which one's usual or expected physical, emotional, social and [functional] well-being is affected by a

medical condition and/or its treatment" (Cella, 1995, p. 73), as measured by a standardized questionnaire.

Significance

Problem solving, planning, learning and goal setting skills may potentially be adversely impacted in the presence of impaired concentration (Olson et al., 2008). "In individuals with cancer, a loss of concentration can reduce ability to learn important information, adhere to complex treatment regimens, and resume valued life roles" (Cimprich, 1995, p. 279). Thus, for the affected patient, this could potentially have implications in a number of areas including: a) adherence to treatment recommendations (e.g., forgetting to take medications as prescribed; difficulty following instructions for self-care such as looking after indwelling intravenous catheters); b) interfering with the ability to make informed decisions regarding treatment options (e.g., difficulty attending to, understanding, and remembering explanations); c) concerns about ability to maintain employment or educational activities; d) reservations about accepting chemotherapy treatment secondary to concerns about developing chemo-brain (Bender et al., 2001; Cimprich, 1995; Grober, 2002; Kibiger, Kirsh, Wall, & Passik, 2003; Nelson, Nandy, & Roth, 2007; Wefel, Kayl & Meyers, 2004). A better understanding of the nature of cognitive impairments in cancer patients could help health care professionals develop interventions to manage cognitive impairment more effectively.

Chapter 2: Literature Review

Search Strategy

A search of the literature was conducted using the following electronic databases: Journals at OVID, CINAHL, Medline (1966 to 2010), AMED, EBM Reviews, PsycInfo, Global Health (1985 to 2010), and Health & Psychosocial Instruments (1985 to 2010). Key words for the search (used individually and in various combinations) included:

> Cognitive impairment; chemo-brain; altered cognition; neuropsychological; memory changes; cognitive changes; cognitive function; assessment; battery; test; brain organization/structures/processes; cancer; chemotherapy; oncology; hematology; and lymphoma.

The reference lists of retrieved articles and abstracts were also reviewed to locate additional relevant references.

Terminology

The terms "chemo brain" and "chemo fog" were coined by cancer patients to describe memory and concentration problems they attributed to adverse effects of chemotherapy (Coyne & Leslie, 2004; Harvard Women's Health Watch, 2002; LaTour, 2002; Oncology News International, 2001; Phillips & Bernhard, 2003). Other terms used in the scientific literature to refer to this phenomenon include: central neurotoxicity, cognitive dysfunction, cognitive impairment, chemotherapy–induced cognitive impairment, neurocognitive (neuropsychological) dysfunction, chemotherapy-related cognitive dysfunction (CRCD), and cognitive dysfunction in cancer patients (CDCP) (Staat & Segatore, 2005; Vetto & Vetto, 2007).

Normal Cognitive Function

Cognition is the general term for the process of thinking and consists of several domains including attention and concentration, information processing speed, memory (verbal and visuospatial), learning, language, executive function, visuospatial skill, and psychomotor ability (Bender, et al., 2001; Jansen, Miaskowski, Dodd, & Dowling, 2005; Kolb & Whishaw, 2009; Minisini, et al. 2004; Nail, 2006; Oxaman, Schnurr, & Silberfarb, 1986). (See Appendix B: Skills Associated with the Various Cognitive Domains). Each of these domains is multidimensional and interrelated. For example, one must first be able to attend to information before learning can take place (Bender et al., 2001)

Cognitive function is the term used to describe intellectual functioning (Baumgartner, 2004) and refers to the ability of the brain to acquire, process, store, and retrieve information (Lawlor, 2002; Oxaman et al., 1986). Human cognition depends on the ability to form long lasting memories and to retrieve those memories when required (Weeber, Levenson & Sweatt, 2002). "Normal cognitive functioning is critical for intellectual and academic development, occupational achievement, development and maintenance of social relationships, and appropriate self-care" (Walch, Ahles, & Saykin, 1998, p. 500), thus allowing individuals to effectively perform activities of daily living and maintain quality of life (McDougall, 2001; O'Shaughnessy, 2003; Oxaman et al., 1986). Cognitive dysfunction is considered to be any decrement in intellectual functioning or specific deficits in cognitive abilities (Baumgartner, 2004; Galantino, Brown, Stricker & Farrar, 2006; Garofalo & Baum, 2001).

Contributors to Cognitive Dysfunction

The etiology of cognitive impairment is multi-factorial in nature. Potential risk factors have generally been divided into direct and indirect factors. Direct factors are those related to the cancer such as primary central nervous system (CNS) tumours, metastases to the CNS, or paraneoplastic syndromes (Bender et al., 2001; Breitbart & Wein, 1998; Staat & Segatore, 2005). Indirect factors include such variables as age, depression, anxiety, medications, infection, anemia, nutritional deficiencies, metabolic or endocrinologic abnormalities, sleep disorders (Bender et al., 2001; Breitbart & Wein; Oxaman et al., 1986; Staat & Segatore, 2005), or genetic factors (Ahles et al., 2003). Using a gardening metaphor, some authors have conceptualized this as an interaction between the seed (effects of the disease), soil (individual or host related factors), and pesticides (the physiological effects of the cancer treatment) (Kean & Locke, 2008; Meyers & Perry, 2008). It is difficult to determine which cognitive dysfunctions are disease-related and which are pharmacologically induced (Kurita, et al., 2009). Additionally, the presence of a number of concurrent, related symptoms, such as fatigue, pain, depression, and sedation may also influence cognitive functioning (Kurita et al., 2009). Any of these factors either alone or in combination may potentially impact cognitive functioning and the severity of any deficits experienced. As a result, the discussion in the remainder of this section is structured around the main factors reported to be associated with CD, and no attempt has been made to distinguish between direct and indirect effects.

Normal aging. Cognitive impairment similar to that described for chemo brain has been reported as part of normal aging and also in patients with chronic illnesses such as

congestive heart failure, diabetes, chronic obstructive pulmonary disease, depression, HIV infection, hepatitis C infection, chronic fatigue syndrome, and acquired brain injury (Bender et al., 2001; Budson & Price, 2005; Raffa et al., 2006; Staat & Segatore, 2005). A general decrease in the efficiency of information processing and retrieval is associated with normal aging with the greatest effect on working memory and episodic memory (Joshi & Morley, 2006). There is a slow progressive impairment over the lifespan with impairment of free recall of stories and word lists (long-term memory) evident by the age of 50 years (Joshi & Morley, 2006). However, short-term memory is generally well preserved unless there is a high demand placed on processing resources (e.g., tasks requiring manipulation of information in the short term such as repeating a string of digits back in reverse order) (Joshi & Morley, 2006).

Memory for past events occurs either through recollection (specific contextual details) or familiarity (feeling that event is old or new without recovery of contextual details): Healthy aging affects recollection more than familiarity (Joshi & Morley, 2006). The hippocampus is involved with recollection, whereas familiarity depends on the perirhinal cortex. "With aging, there occurs a reduced functional connectivity within a hippocampal-retrosplenial/parietotemporal network but increased connectivity within a [peri]rhinal-frontal network. These findings indicate that older adults compensate for hippocampal deficits by relying more on the [peri]rhinal cortex, possibly through a top-down frontal modulation [with potential] clinical implications [given that] the hippocampus and [peri]rhinal cortex is (sic) impaired in early Alzheimer's disease (AD)" (Joshi & Morley, 2006, p.770).

"Mild cognitive impairment" (MCI) has been identified as a discrete disorder representing a boundary or transitional state between normal aging and dementia (specifically Alzheimer's disease) (Petersen et al., 1999). It is characterized by memory impairment beyond that expected for age and education, but with normal activities of daily living, normal general cognitive functioning and without dementia. The presence of MCI in an individual is associated with a 1% - 25% per year increased risk for the development of AD (Petersen et al., 1999). Depending on the study, the prevalence of MCI in a community dwelling population is estimated between 5% - 25% and between 6% - 85% of those in a clinical setting (Joshi & Morley, 2006). The incidence of MCI in cancer patients is unknown (Baumgartner, 2004); however, with the aging population could conceivably be expected to occur at a similar rate as in the general (non-cancer) population.

Anemia. Anemia is a common finding in patients with cancer, with the prevalence increasing in those over 65 years (Mancuso, Migliorino, De Santis, Saponiero, & De Marinis, 2006), and as a consequence of chemotherapy (O'Shaughnessy, 2003). A correlation between anemia and deficits in attention span, learning and memory has been observed in the chronic renal dialysis population (Mancuso et al. 2006; Meyers, 2000). Changes in measures of event related potentials (ERPs) (direct electrophysiological measure of brain functioning) have been associated with anemia in end-stage renal disease. Improved performance on measures of attention and working memory and improvement in the ERP was documented when the anemia was corrected in these patients (Friedman & Fernandez, 2008). Artificially induced anemia in healthy adults produced similar deficits both on neuropsychological testing and ERP as seen in the renal failure population, which was reversed following transfusion of fresh or stored autologous

erythrocytes (Friedman & Fernandez, 2008). Erythropoietin is thought to have some neuroprotective effects (Cunningham, 2003); however, studies assessing the effect of erythropoietin on cognitive functioning have been inconclusive (Massa, Madeddu, Laussa, Garmignano, & Mantovani, 2006; Mancuso et al., 2006; O'Shaughnessy et al., 2005).

Pain. Patients experiencing pain show evidence of cognitive impairment in the areas of attention and concentration, multitasking, speed and efficiency of thinking (Meyers, 2000), and memory (Lawlor, 2002). The use of sedating medications may also contribute to cognitive problems. Although sedation and cognitive impairment can occur at the time of initiation of opioid therapy and following a dose increase, studies have shown no association between the use of chronic stable doses of opioids and neuropsychological test impairment (Cimprich, 1995; Lawlor, 2002). Kurita et al. (2009) conducted a systematic review of 10 controlled studies (two randomized trials, two non-randomized trials, five cross-sectional studies, and one case-control study) that used neuropsychological measures to assess the cognitive effects of opioids in cancer patients. They report that although the majority of studies showed minor cognitive deficits associated with long-term opioid use, increased dose and supplemental doses of short-acting opioids were associated with cognitive impairment. The authors found a wide variability in study design and neuropsychological tests used and as such stated that the 'specific nature and the quality of the cognitive impairment are still unclear" (Kurita et al., 2009, p.20).

Fatigue. Fatigue is one of the most common symptoms associated with cancer and cancer therapy (Valentine & Meyers, 2001), and may be either physical or mental

(Meyers, 2000). Physical fatigue is reduced stamina or energy to perform usual daily activities, whereas mental fatigue results in patients becoming easily overwhelmed, having difficulty organizing and efficiently completing daily activities (Meyers, 2000). Impairment in cognitive functioning includes loss of concentration and attention, increased distractibility, and impaired perception and thinking, and can result in a reduced capacity to perform activities requiring mental effort (Cimprich, 1995; Meyers, 2000; Winningham et al., 1994). Directed attention is the ability to focus and concentrate, requires mental effort to sustain, and is considered susceptible to fatigue (Cimprich, 1995). Fatigue of the underlying neural mechanisms that act to block competing or distracting stimuli can result from prolonged or intense exertion of mental effort (Cimprich, 1992, 1993; Olson et al., 2008; Winningham et al., 1994). Thus, prolonged or intense use of directed attention over an extended time can lead to 'attentional fatigue' (Cimprich, 1992; 1995), exacerbating any existing impairment in cognitive functioning (Cimprich & Ronis, 2003). The mental demands and acute stress reaction associated with a diagnosis of cancer and its' treatment can place these patients at high risk for the development of attentional fatigue (Cimprich, 1995; Meyers, 2000), "negatively affect[ing] patients' ability to focus, concentrate, and organize activities, leading to complaints of forgetfulness and other cognitive problems" (Meyers, 2000, p. 76).

Genetic factors. The apolipoprotein E ε4 (APOE ε4) gene has been proposed as one potential risk factor for chemotherapy-induced cognitive decline. It has been associated with: a) an increased risk of development of Alzheimer's disease; and b) neuropsychological deficits following cardiac bypass surgery, traumatic brain injury and repeated head trauma associated with football and boxing; as well as being a moderating

factor of other risk factors (e.g., diabetes) for cognitive decline in the elderly. Previous animal and human studies have shown decreased functioning in the visual/spatial domains for APOE ε4 carriers (Ahles et al., 2003).

Chemotherapeutic, biologic and hormonal agents. Neurological complications of chemotherapeutic, biologic and hormonal agents used for treatment of cancer are common (Dropcho, 2004; New, 2005; Wefel, Kayl, et al, 2004). Treatment-related complications generally take the form of central neurological toxic effects (Minisini et al., 2004; New, 2005), peripheral neuropathies, acute encephalopathy (confusion, insomnia, agitation that resolves when treatment is stopped), chronic encephalopathy (dementia, incontinence, gait disturbance), leukoencephalopathy, ototoxicity, or cerebellar symptoms (ataxia, pancerebellar syndrome) (Dropcho, 2004; Walch et al., 1998; Wefel, Kayl, et al., 2004). However, other than a few drugs such as corticosteroids, biologic response modifiers and possibly the sex hormones/antagonists, the effect of anti-cancer agents on neurocognitive functioning is not well established.

Corticosteroids. The most frequent manifestation of corticosteroid-induced cognitive dysfunction includes impairment of the domains of memory, concentration and attention. Conditions with sustained endogenous hypercortisolemia (e.g., Cushing's disease, depression, aging) are often associated with explicit (declarative) memory impairment (Coluccia et al., 2008; Young, Sahakian, Robbins, & Cowen, 1999). The deficits associated with chronic glucocorticoid exposure are thought to be related to cumulative and long-lasting influences on the hippocampus including altered adrenal steroid receptor density, neurotransmitter content and dendritic (hippocampal) atrophy

(Coluccia et al., 2008; Young et al., 1999). “Acutely elevated glucocorticoid levels at the time of retention testing impair the retrieval of previously acquired information [but this effect is] limited to the time that circulating hormone levels are elevated” (Coluccia et al., 2008, p.3474).

Potential toxicities of high dose steroids may result in deficits in attention, verbal memory, and psychomotor speed (New, 2005). Pulse high dose steroids (dexamethasone or prednisone) are typically used in combination with other cytotoxic agents for the treatment of lymphoma and multiple myeloma, and lower doses are often used in other patient populations for the control of chemotherapy related nausea/vomiting. The potential effect of these drugs must therefore, be considered when assessing cognitive function in cancer patients.

Biologic response modifiers. At least 50% of patients receiving the biologic response modifier, interferon-α (INF-α), may experience psychomotor slowing, impaired memory, impaired concentration, speech impairment, and mood changes, all of which generally resolve with cessation of therapy (Meyers, 2000; Minisini et al.; 2004, Walch et al., 1998). These deficits may be significant enough to interfere with activities of daily living including occupational pursuits, and may be exacerbated with high cumulative doses or concurrent chemotherapy (Friedman & Fernandez, 2008). The executive and information processing dysfunction that occurs with INF-α is consistent with frontal-subcortical pathology, and similarly to Parkinson’s disease, extrapyramidal symptoms (rigidity, tremour and masked facies) have been reported in some patients receiving INF-α (Friedman & Fernandez, 2008). Whereas adverse effects such as decreased appetite and

fatigue appear around the second week of treatment, mood and cognitive changes become apparent between 8 to 12 weeks after initiation of therapy. Neuropsychological impairments may persist up to 2 years after discontinuation of the treatment: It has been suggested that some of these changes may be permanent and not reversible (Friedman & Fernandez, 2008). With the development of newer agents for treating hematological and renal malignancies, INF-α is used much less frequently than previously. However, it continues to be used as front-line therapy in melanoma and therefore, may potentially contribute to cognitive impairment in this patient population.

Gonadotrophic hormones. Fluctuating hormone levels have been shown to have an effect on cognitive functioning in both women and men. During the menstrual cycle, higher levels of estrogen have been associated with reduced spatial ability, whereas articulation and motor capability are enhanced (Kolb & Whishaw, 2009). Estrogen affects catecholamine levels (e.g., epinephrine and dopamine); there are dopamine receptors in the prefrontal cortex and the medial temporal region and as such it is possible that estrogen may have an effect on and alter the functioning of these areas (Kolb & Whishaw, 2009), resulting in changes in cognitive abilities. Functional magnetic resonance imaging (fMRI) studies in women have shown increased blood oxygenation in response to arousing stimuli in a number of cerebral regions (amygdala, hippocampus, frontal lobe) at the low estrogen point of the menstrual cycle compared to the high estrogen time-point which may contribute to fluctuation in mood and anxiety levels and cognitive function (Kolb & Whishaw, 2009).

Estrogen has direct effects on the structure of neurons with the number of dendritic spines and thus the number of synapses on hippocampal neurons varying greatly during the female rat's estrous cycle, with fewer spines during the low estrogen period. This finding, as well as an increase in dendrites and spines of cortical neurons in female rats whose ovaries are moved in middle age is consistent with the hypothesis that estrogen has direct effects on cerebral neurons in the adult animal; similar changes are thought to take place in the human brain (Kolb & Whishaw, 2009).

Testosterone levels in men fluctuate daily and seasonally, with levels being highest in the autumn and morning, compared to spring and evening respectively (Kolb & Whishaw, 2009). Men perform better on spatial tests and mathematical reasoning tests when the levels are low (i.e., in the spring and evening) (Kolb & Whishaw, 2009).

Based on the observation of an association between depletion of normal hormone levels (as in menopause in women and after the age of 50 in men) and reduced attention, learning, and memory, it has been proposed that the gonadotrophic hormones (estrogen, progesterone, and testosterone) have neuroprotective effects (Ahles & Saykin, 2001; Bender et al., 2001). Although a number of studies have shown that verbal fluency and verbal and spatial memory is improved by estrogen therapy in postmenopausal women, the large Women's Health Initiative study failed to support these cognitive findings (Kolb & Whishaw, 2009). It has been hypothesized that for estrogen replacement therapy to provide maximal beneficial effects on cognition it needs to be initiated close in time to natural or surgical menopause and that beginning treatment 20 years after menopause is too late and of no benefit (Kolb & Whishaw, 2009), "One explanation is that, although

estrogen is neuroprotective, neurons become less sensitive to it after a prolonged absence of the hormone. Another explanation is that so many neurons have died or atrophied in the absence of estrogen that it is not possible to reverse the effect of aging" (Kolb & Whishaw, 2009, p.330). Spatial cognition and verbal memory in older men may be enhanced with the administration of exogenous testosterone (e.g., estradiol, a metabolite of testosterone) (Kolb & Whishaw, 2009).

Chemically-induced hormone ablation therapy in patients with breast and prostate cancers may have a negative effect on cognitive function (Ahles, 2004; Bender et al., 2001; Meyers, 2000; Minisini et al. 2004); however, further research is needed to evaluate the effects of hormone manipulation strategies as the published studies have reported inconsistent and conflicting results (Nail, 2006).

Studies of Cognitive Dysfunction in Cancer Patients

The majority of research studies have investigated cognitive functioning in female breast cancer patients treated with adjuvant chemotherapy. Depending on the study, anywhere from 16% to 75% of these patients were reported to experience cognitive deficits (Ahles et al., 2002; Brezden et al., 2000; Hurria et al., 2006; Schagen et al., 1999; Tchen et al., 2003; van Dam et al., 1998; Wieneke & Dienst, 1995).

Small numbers of adult patients with other types of cancer have been included in a few studies: lung cancer (Meyers, Bryne & Komaki, 1995; Whitney et al., 2008); Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) (Ahles et al., 2002; Ahles et al., 2003; Cull et al., 1996; Devlen, Maguire, Phillips, Crowther, & Chambers, 1987a, 1987b); acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS)

(Meyers, Albitar, & Estey, 2005); prostate carcinoma (Cherrier, Aubin, & Higano, 2009; Salminen, Portin, Koskinen, Helenius, & Nurmi, 2005); and bone marrow (haematopoietic stem cell) transplant patients (Andrykowski et al., 1992; Harder, Duivenvoorden, van Gool, Cornelissen, & van den Bent, 2006).

The majority of the studies have been cross-sectional in design with one neuropsychological assessment taking place anywhere between 6 months to 10 years following treatment (Ahles et al., 2002; Ahles et al., 2003; Brezden et al., 2000; Schagen et al., 1999; van Dam et al., 1998; Wieneke & Dienst, 1995). However, longitudinal studies are now underway, some of which are beginning to be published (e.g., Bender et al., 2006; Cherrier et al., 2009; Salminen, et al., 2005; Schagen et al., 2002).

Bender et al. (2006) evaluated cognitive function at three time-points in women receiving adjuvant therapy for breast cancer: 1) following surgery and before the start of chemotherapy; 2) within 1 week after completion of chemotherapy; and 3) 1 year after the second assessment. Patients with ductal carcinoma *in situ* not receiving chemotherapy were assessed at comparable time-points. Deterioration in memory over time was found in women who received adjuvant chemotherapy; whereas, the women who did not receive chemotherapy had an improvement in cognitive function scores (the authors attribute this latter finding to practice effect).

Twenty-three men with prostate carcinoma on androgen deprivation therapy were tested prior to the start of treatment, and again at 6 and 12 months of therapy (Salimen et al., 2005). The results suggested a marginal, but selective association between testosterone

decline, estradiol, and cognitive performance, specifically the domains of verbal fluency, visual recognition and visual memory.

Schagen et al. (1999) and van Dam et al. (1998) originally performed cognitive testing 2 years after completion of treatment in breast cancer patients who had received chemotherapy. Schagen et al. (2002) conducted a second assessment in those patients whose disease was still in remission 2 years later (i.e., 4 years post chemotherapy) to assess neuropsychological functioning over time. The authors found an improvement in cognitive function at the second testing, and suggested that cognitive dysfunction in breast cancer patients following adjuvant chemotherapy may be transient.

The most frequently reported deficits following chemotherapy relate to difficulty with attention and concentration, learning new information and recalling recently learned information (Bender et al., 2001). Global decline was documented in all cognitive domains except for the areas of abstract reasoning and verbal fluency in a group of breast cancer patients tested following completion of adjuvant breast cancer chemotherapy (Wieneke & Dienst, 1995).

Four meta-analyses have recently been reported in the literature. Two of these looked at studies of breast cancer patients (Falleti et al., 2005; Stewart, Bielajew, Collins, Parkinson & Tomiak, 2006) while the other two included studies of patients with various malignancies (Anderson-Hanley et al., 2003; Jansen, Miaskowski, Dodd, Dowling, & Kramer, 2005a). The majority of the studies reviewed by these meta-analyses are cross-sectional in design with *across* subject comparisons. A few longitudinal studies using *within*-subject comparisons were also reviewed (Anderson-Hanley et al., 2003 – seven

studies; Falleti et al., 2005 – one study; Jansen et al., 2005a - four studies; Stewart et al., 2006 – one study). However, it should be noted that due to the limited number of trials that have been completed evaluating cognitive function and chemotherapy, all four meta-analyses have a number of studies in common on which they conducted their analyses.

All four meta-analyses found significant negative effect sizes of small to moderate magnitude in the domains of language, memory, spatial ability, information processing speed, and psychomotor abilities in chemotherapy patients when compared to normative samples or control groups. However, the decline was only ¼ to ½ standard deviation (SD) (Stewart et al., 2006) to ⅓ to 1 SD (Anderson-Hanley et al., 2003) below that of the normative samples or control groups. This level of decline would not necessarily be expected to result in easily observable functional difficulties in most patients (i.e., subtle changes) (Anderson-Hanley et al., 2003). Interestingly, when patients' results were compared to their own baseline, an improvement (Falleti et al., 2005) or no significant change (Jansen, Miaskowski, Dodd, Dowling, & Kramer, 2005a) was found. Falleti et al. (2005) note the improvement in cognitive function is inconsistent with most of the cross-sectional studies which show a decline, and they speculate that the psychological burden, stress and depression associated with a diagnosis of breast cancer is reduced by initiation of curative treatment. Other possible explanations they propose are the effects of practice and learning on test outcomes, or normal variability in performance over time. Jansen, Miaskowski, Dodd, Dowling, & Kramer (2005a) speculate that possible reasons for no change being noted between baseline and testing after chemotherapy may be related to preexisting cognitive impairment and/or the effects of learning and practice on neuropsychological retesting.

Even though neuropsychological test scores in a number of studies were significantly lower in chemotherapy-treated patients compared to control patients who did not receive chemotherapy, when compared with published reference norms, performance was within the normal range, indicating subtle cognitive change (Ahles et al., 2002; Ahles et al., 2003; Schagen et al., 1999; van Dam et al., 1998).

The studies found no correlation between anxiety, depression, fatigue (Ahles et al., 2002; Bender et al., 2006; Brezden et al., 2000; Grober, 2002; Jansen, Miaskowski, Dodd, & Dowling, 2005; Tchen et al., 2003; Wieneke & Dienst, 1995), type of chemotherapy, time since final chemotherapy treatment (Tchen et al., 2003; Wieneke & Dienst, 1995), or menopausal status (Tchen et al.; Wefel, Lenzi, et al., 2004) and cognitive changes. Wieneke and Dienst (1995) found a possible relationship to length of chemotherapy treatment, with those receiving treatment for a longer duration experiencing more cognitive impairment. However, Tchen et al. (2003) did not find a correlation between the duration of chemotherapy and cognitive dysfunction.

A relationship between cognitive impairment and dose of chemotherapy was found in a cross-sectional study by van Dam et al. (1998). At an average of 2 years post chemotherapy, 32% of women treated with high dose chemotherapy for high risk breast cancer were cognitively impaired, compared to 17% of those treated with standard dose chemotherapy, and 9% of the control patients (early stage breast cancer patients who did not receive chemotherapy). Compared to the control patients, there was an 8.2 times higher risk for development of cognitive impairment with high dose chemotherapy, and a 3.5 times higher risk with standard dose chemotherapy.

The duration of cognitive impairment following chemotherapy is not known. It has been suggested that a subgroup of cancer survivors may have long-term cognitive deficits. For example, in a group of breast cancer and lymphoma patients who were tested on average approximately 10 years following completion of treatment, those who had received chemotherapy scored significantly lower in the domains of verbal and psychomotor functioning than did those treated with local (surgery or radiation) therapy (Ahles et al., 2002).

On the other hand, Schagen et al. (2002) suggest the effect may be transitory. Improvements in cognitive functioning were seen in a follow-up study of breast cancer patients who had been treated with chemotherapy 4 years previously and in whom cognitive impairments were documented by neuropsychological testing 2 years following chemotherapy (Schagen et al., 1999; van Dam et al., 1998).

Historically, the assumption was made that cognitive changes seen after chemotherapy were related to side effects of the anti-cancer drugs (ONS News, 2004); however, research has documented cognitive deficits in some patients prior to initiation of any chemotherapy treatment. Approximately 35% of women with breast cancer (Wefel, Lenzi, et al., 2004), up to 40% of patients with AML/MDS (Meyers et al., 2005), 70% of small cell lung cancer (SCLC) patients (Meyers et al., 1995), and 40% of elderly cancer patients over the age of 65 years (Massa et al., 2006) showed baseline evidence of cognitive impairment on neuropsychological testing. The domains affected were verbal learning and memory (Meyers et al., 1995; Meyers et al., 2005; Wefel, Lenzi, et al., 2004), executive function and motor function (Meyers et al., 1995; Meyers et al., 2005), and

cognitive processing speed (Meyers et al., 2005). In the study by Massa et al. (2006), cognitive function was assessed using the MMSE, therefore, given the general nature of this test, the specific domains which might have been affected could not be identified: Cognitive function is assessed as either "normal," "moderately" impaired, or "severely" impaired. The authors speculate that the preexisting cognitive deficits were related to both disease factors (Massa et al., 2006; Meyers et al., 1995; Meyers et al., 2005; Wefel, Lenzi, et al., 2004) and host factors (Wefel, Lenzi, et al., 2004).

In a study by Ahles et al. (2003), 17 (21%) of 51 cancer survivors who were at least 5 years following diagnosis with breast cancer or lymphoma were found to carry at least one APOE ε4 allele. Significantly lower scores in the visual memory and spatial ability domains on neuropsychological testing were found in these patients compared to those survivors without one APOE ε4 allele. Consistent with other studies the results of both groups were within the normal range compared to reference ranges (Ahles et al., 2003). The authors suggest that APOE status may be a risk factor for long-term cognitive problems in a subset of patients treated with standard dose chemotherapy. Therefore, future studies into chemotherapy-induced cognitive dysfunction may need to consider incorporating testing for the APOE ε4 gene to confirm if there is any association between these factors.

Gaps in the Literature

Despite the research that has been completed to date, the characteristics and impact of cognitive dysfunction in cancer patients following chemotherapy are still not well understood (Saykin & Ahles, 2000). Although the generalizability of the studies is

limited, the majority confirms the experience of cognitive dysfunction and supports ongoing study of this potential side effect (Staat & Segatore, 2005). It is estimated that approximately 20% of patients will manifest measurable cognitive deficits on neuropsychological testing post chemotherapy (Meyers, 2000; Saykin & Ahles, 2000). Given the increasing incidence of cancer, this could potentially translate into significant numbers of patients being at risk. In order for health care professionals to be able to provide comprehensive education and support to their patients with the objective of reducing the potential morbidity of the treatment, a better understanding of the incidence, duration, symptoms, and risk factors, as well as the potential impact of cognitive deficits on the patient is of utmost importance.

As noted above, the majority of studies conducted to date have been cross-sectional in design, making it difficult to know if some of the changes documented after completion of the chemotherapy may actually have been present at baseline, prior to initiation of the treatment. Comparisons have been *across* subjects, rather than *within*-subjects: Prospective longitudinal studies using objective measurements will be required to determine the frequency of cognitive deficits prior to treatment, as well as during and following completion of therapy. Without baseline data the true incidence of decline in cognitive functioning secondary to chemotherapy may be over estimated (Wefel, Lenzi, et al., 2004).

The effects documented on neuropsychological testing have generally been subtle and do not necessarily correlate with the individual's self-reported cognitive functioning. "Measuring a patient's report of *perceived* change may add to our understanding of …

subtle cognitive change and its impact on daily activity" (Galantino et al., 2006, p.16). Therefore, both subjective and objective testing measures should be incorporated into study designs. Dysfunction of fronto-subcortical networks is suggested by the pattern of cognitive deficits seen in patients undergoing chemotherapy: These areas mediate executive function, processing speed, inhibition, and goal directed behavior (Kean & Locke, 2008; Taillibert, Voillery, & Bernard-Marty, 2007); therefore, the specific battery of neuropsychological tests utilized to assess CD in this patient population should be chosen to ensure that at minimum these cognitive domains are evaluated.

Whereas the majority of studies have been in breast cancer patients, similar effects have been documented in patients with other malignancies. Differences in disease presentations, symptoms, potential confounding risk factors, and chemotherapy drugs all may have an impact on cognitive function, which may not be the same as in women receiving adjuvant treatment for breast cancer. Thus, additional information on the impact of chemotherapy on cognitive function in patients with diagnoses other than breast cancer is clearly needed.

Chapter 3: Methods

Research Design

A quantitative, descriptive, prospective, observational design was utilized in the conduct of this study. A study into the possible effects of chemotherapy on cognitive functioning lends itself to a quantitative design given that standardized instruments are available for measuring the variables of interest (Brink & Wood, 1998). The majority of previous studies into CD in cancer patients have used a cross-sectional design; therefore, little information is available with respect to cognitive changes that occur in individuals currently receiving chemotherapy. Longitudinal designs are appropriate for studying the dynamics of a phenomenon over time (Polit & Beck, 2004) and as such, this was the design chosen for this study. Beginning prior to the initiation of chemotherapy, the dependent variable, cognitive function, was measured at multiple time-points in each subject to enhance the interpretability of the results (Polit & Beck, 2004). A *within*-subject comparison of the cognitive function test scores obtained prior to start of chemotherapy, during the course of chemotherapy, and after the completion of chemotherapy will be performed at the completion of all study assessments. In this study there was one dependent variable of interest (cognitive function) and one independent variable (chemotherapy). Possible confounding variables (e.g., fatigue, depression, anxiety, age, education) were controlled for through rigorous collection of data and statistical techniques.

Study Setting and Sample

Setting. The setting for the study was the Cross Cancer Institute (CCI), a comprehensive tertiary cancer care facility located in Edmonton, Alberta. The geographic area served by the CCI includes the northern half of the province from Red Deer north, as well as parts of northeastern British Columbia, western Saskatchewan, and the Northwest Territories. The majority of newly diagnosed lymphoma patients residing within this geographic region are seen in consultation at the CCI, at which time a treatment plan is recommended. Chemotherapy for lymphoma is administered on an outpatient basis in the Medical Day Care Unit. Patients are seen in the Outpatient Department (OPD) of the CCI on the day prior to their scheduled chemotherapy for assessment in order to confirm they meet the criteria to proceed with their next cycle of chemotherapy on schedule.

Alberta Health Services – CancerControl Alberta (formally Alberta Cancer Board), in addition to operating two tertiary cancer centres (CCI and Tom Baker Cancer Centre (TBCC) in Calgary), also operates 4 associate cancer centres and 12 community cancer centres throughout Alberta. Patients who live a distance from Edmonton may receive standard chemotherapy at either an associate or community cancer centre. Although the majority of lymphoma patients receive their treatments at the CCI, some receive treatment at one of the other centres closer to home. Consequently, patients being treated at centres other than the CCI may have been potentially unavailable for participation in this study due to geographic distance from the study site.

Sample.

Target population. The target population was non-Hodgkin's lymphoma (NHL) patients receiving frontline chemotherapy for their disease.

Accessible population. The accessible population was NHL patients who were receiving their initial chemotherapy regimen at the CCI. It was estimated that approximately 670 new lymphoma cases would be diagnosed in Alberta in 2010 (Canadian Cancer Society/National Cancer Institute of Canada, 2010). Approximately one half of these or 330 patients would have been seen in consultation per year at the CCI, with the remainder being seen at the TBCC which serves the southern half of the province. Of the 330 patients seen at the CCI, a conservative estimate of the number receiving chemotherapy per year was 140 to 165. Given that not all of these patients would meet the eligibility criteria for this study, it was estimated the potential patient population per year would be in the range of 70 to 90 patients. Additional patients were potentially available from the low grade, indolent lymphoma histology population who did not require treatment at the time of their initial diagnosis and were being followed on a "wait and watch" policy, but whose disease became symptomatic and who thus required chemotherapy (a conservative estimate was 10 to 15 such patients in 1 year). Patients receiving chemotherapy at either an associate or community cancer centre were potentially eligible to participate in this study provided they were willing to travel to the CCI for testing at the time-points as specified in the research protocol.

Sample size. The ideal sample would be one that is randomly chosen (Brink & Wood, 1998), but, as this sampling method was not possible in this setting due to a limited

patient population, a non-probability, systematic sample (k = 1) (Wood & Ross-Kerr, 2006) was utilized for this study. All patients who met the eligibility criteria were approached regarding participation in the study.

The required sample size was calculated using the effect sizes reported in four meta-analyses (Anderson-Hanley et al., 2003; Falleti et al, 2005; Jansen, Miaskowski, Dodd, Dowling, & Kramer, 2005; Stewart et al., 2006). All four meta-analyses found small to medium negative effect sizes (range: -0.13 to -0.70) for most of the cognitive domains tested, although Anderson-Hanley et al. (2003) reported a large negative effect size (-0.90) for both of the domains of verbal memory and executive function. Sample size calculations were determined in collaboration with Sunita Ghosh (Ph.D., P.Stat.), Assistant Clinical Professor, Department of Oncology, University of Alberta and Senior Research Biostatistician Alberta Health Services – CancerControl Alberta (Personal communication June 2, 2010). Using a two-tailed t-test at power of 0.80, alpha of 0.05, a moderate effect size of 0.50, and three data collection time-points a sample size of 92 participants would be required, using five data collection time-points the sample size would be 85 participants. However, if the effect size was small (0.20) a sample size of 574 participants would be required for three time-points and 533 for five time-points. (See Appendix C for table of complete sample size calculations). To accrue such a large number of participants within a reasonable time period, a multi-centre study would be necessary; however, such a study was not feasible in this instance, given that this was a PhD thesis research study being conducted by the principal investigator. In addition, to ensure the study was completed within a reasonable time frame for the purposes of my dissertation, I planned to accrue based on a moderate effect size and 5 data collection time points (85 participants).

This study aimed to accrue a minimum of 100 patients with NHL who were receiving front-line chemotherapy. This represented an approximate increase of 15% to adjust for possible attrition.

Eligibility criteria.

Inclusion criteria.

1. Patients with a diagnosis of non-Hodgkin's lymphoma who were scheduled to receive initial (frontline) chemotherapy
2. No chemotherapy within the previous 5 years
3. Adult patients aged 18 years or older
4. Male and female
5. Ability to read and understand English (i.e., the testing instruments are in English)
6. ECOG performance status (PS) 0 - 2 (see Appendix D). An upper limit of 2 was placed on PS, as patients with a worse PS (i.e., level 3 or 4), may potentially have pre-existing cognitive impairment related to either disease or other factors that may make assessment of cognitive function and interpretation of any changes that occur difficult. In addition, patients with a worse PS may have been unable (or unwilling) to complete the required testing procedures, which can be time consuming.
7. Geographic proximity to the CCI in order to be available for testing at required time-points
8. Signed written informed consent

Exclusion criteria.

1. Primary CNS (central nervous system) lymphoma
2. Known CNS involvement by lymphoma
3. Known diseases or injuries that could potentially affect cognition (e.g., Alzheimer's disease, early dementia, major depression, mental illness, stroke, head injury, drug, or alcohol abuse)
4. History of another malignancy for which they had been treated with chemotherapy within the previous 5 years
5. Prior history of cranial irradiation

Plans for Study Recruitment

In order to ensure that I was aware of all potentially eligible patients, the following action plan was implemented:

1. I met with the medical and nursing staff prior to initiation of the study to ensure they were all aware of the study. This was done at regularly scheduled meetings, such as the weekly lymphoma rounds, monthly hematology tumour group research meetings, e-mail notices/reminders, and meeting individually with the relevant medical and nursing personnel.
2. I provided all relevant medical and nursing staff with a written synopsis of the study including purpose, inclusion and exclusion criteria, and my contact information.
3. I attended the OPD lymphoma clinics to check if any new patients were scheduled for that day. In addition, simply being visible in clinic and available

to answer any of the health care professionals' questions helped to remind them to think of this study when seeing newly diagnosed lymphoma patients.

4. All new lymphoma cases are presented at weekly lymphoma rounds; therefore, this was an opportunity to be made aware of potential patients that I had not heard about through other means. The only potential issue with this option was that occasionally patients had already been started on treatment prior to their case being presented at these rounds.

When a potential patient indicated an interest in the study, I approached the patient to introduce myself, and provide an explanation of the study including the purpose of the study, type and frequency of testing, how long the testing at each time-point was expected to take, when and where the testing would be done, the voluntary nature of participation in the study, how confidentiality would be maintained, etc.

The patient was provided with a copy of the written informed consent document (attached in Appendix F) and provided with time to review it, discuss with family/friends, and have his/her questions answered. An appointment time was made to either see the patient back in clinic or arrange for phone contact to answer any other questions he/she had and to obtain his/her decision regarding participation in the study. A potential limitation to the length of time allowed for patient review was dictated by the scheduled chemotherapy start date (i.e., the patient was required to make a decision regarding study participation prior to this in order to allow for completion of the pretreatment baseline testing). If the patient agreed to participate, he/she was asked to sign the informed consent, and was provided with a copy of the signed informed consent for reference at home.

Appointments were scheduled to obtain the baseline testing prior to the start of the chemotherapy.

Data Collection

Interval, nominal and ordinal data were collected and included: Demographic, disease and treatment specific information; patient-reported outcome measures; and subjective and objective measurements of cognitive function. Standardized instruments were used for data collection to allow for comparisons to be made (Wood & Ross-Kerr, 2006).

Demographic, disease and treatment specific data. Demographic, disease and treatment specific information was obtained from the patient's health record. This included date of birth, sex, date of lymphoma diagnosis, specific histology, stage of disease, prognostic risk factors (FLIPI for follicular lymphoma [Solal-Céligny et al., 2004], IPI for diffuse large B cell lymphoma [International Non-Hodgkin's Lymphoma Prognostic Factors Project, 1993], MIPI for mantle cell lymphoma [Hoster et al., 2008], ISSWM for Waldenström's macroglobinemia [Morel et al., 2009], Hodgkin Lymphoma IPS for advanced stage disease [Hasenclever & Diehl, 1998], and MD Anderson Cancer Center CLL Prognostic Score [Wierda et al. 2011]), dates of chemotherapy, total number of cycles of chemotherapy administered, the specific chemotherapy regimen administered, concomitant medications, hemoglobin levels, and symptoms. Any additional information that was not in the medical record (e.g., educational level, handedness) was elicited from the patient at the time of consent to participate in the study and as necessary during the course of the study (copy of Data Collection Worksheet attached in Appendix G).

Patient-Reported Outcome Measures. Information on other confounding factors such as the presence and level of fatigue, depression, anxiety, and stress was collected via standardized questionnaires (patient-reported outcome (PRO) measures) (Lipscomb, Gotay, & Snyder, 2007; Sprangers, 2010) as these symptoms may have a contributing role in the development of cognitive dysfunction (Ahles & Saykin, 2001; Minisini et al., 2004).

Anxiety, depression, and stress. There has been no consistent measurement scale used to assess anxiety, depression, and stress in the studies of chemotherapy related CD, with some studies using separate instruments to measure each of these symptoms, whereas in other studies only anxiety or depression was evaluated. The Depression Anxiety Stress Scales (DASS) (Lovibond & Lovibond, 1995) is a set of three self-report scales developed to distinguish between the related emotional states of anxiety, depression, and stress, and is based on a dimensional rather than a categorical conception of each of these syndromes (i.e., they vary on a continuum of severity) (Antony, Bieling, Cox, Enns, & Swinson, 1998; DASS website). Other scales used for measuring depression (e.g., Beck Depression Inventory [BDI] and Zung Self-Rating Depression Scale [SDS]) include somatic symptoms which may be more related to the underlying illness and its' treatment rather than depression, and thus may result in overestimation of the prevalence of depression in clinical populations (Taylor, Lovibond, Nicholas, Cayley, & Wilson, 2005). Somatic symptoms are not included in the DASS.

There are two versions of the scale: The original DASS with 42 questions (14 questions in each of the areas of depression, anxiety, and stress) and a shorter version,

DASS-21 with 21 questions (7 questions assessing each of these areas). Respondents rate each question on a four-point scale indicating the severity/frequency they have experienced each state over the past week (0 – *did not apply to me at all* - to 3 – *applied to me very much, or most of the time*) (DASS website). The depression, anxiety, and stress scales are scored separately, with higher scores indicating higher levels of the respective symptom. The DASS manual (Lovibond & Lovibond, 2004) sets out the criteria for determining the severity of each of the symptoms based on responses to the items on the questionnaire. A total score can be obtained by averaging the Z scores of the three scales to provide a measure of general psychological distress (DASS website; Henry & Crawford, 2005). There are 5 severity ratings: Normal, mild, moderate, severe and extremely severe. The cut-off scores for the severity ratings for each of the subscales are as follows:

	Depression	Anxiety	Stress
Normal	0 – 9	0 – 7	0 -14
Mild	10 -13	8 – 9	15 – 18
Moderate	14 – 20	10 - 14	19 – 25
Severe	21 – 27	15 – 19	26 – 33
Extremely severe	28 +	20 +	34 +

Both the DASS and the DASS-21 are reported to show good psychometric properties with reliability coefficients of Cronbach's alpha of 0.87 - 0.95 (Depression scale), 0.69 - 0.92 (Anxiety scale), 0.89 - 0.95 (Stress scale), and 0.93 - 0.97 (total score) (Antony et al., 1998; Crawford & Henry, 2003; Gloster et al., 2008; Henry & Crawford, 2005; Taylor et al, 2005). Lovibond and Lovibond (1995) reported Cronbach's alpha values for the 7 item scales (i.e. DASS-21) based on a sample of 717 normal subjects of 0.81 (Depression), 0.73 (Anxiety), and 0.81 (Stress). In comparison with other validated

measures of depression and anxiety the DASS-21 has good convergent and discriminant validity (Gloster et al., 2008; Henry & Crawford, 2005). The demographic variables of sex, occupation, education, and age do not have an effect on DASS scores (Crawford & Henry, 2003).

Although I was unable to find references to the use of the DASS or the DASS-21 in the cancer population, the DASS website states "It is unlikely that the factor structure will vary from one group to another. Norms are irrelevant for most special populations … because there is no way of defining the particular group in a way that will transcend culture, health services, severity, etc. Therefore, the most substantive issue to consider is whether the group in question is capable of understanding the items and responding to them in an unbiased way. In this respect, the DASS is no different from other symptom-based measures." Therefore, I did not foresee any reasons why the DASS-21 would be invalid for use in this study population of NHL patients. I calculated the Cronbach's alpha on each scale and on the total score in the current study for comparison to the scores reported in the literature as noted above (see chapter 4 for results).

The DASS-21 (Appendix H) can be completed in approximately 5 minutes (Lam, Michalak, & Swinson, 2005). An advantage of using the DASS is that it reduces the time burden for the patients, since they only have to complete one questionnaire, rather than a separate one for each of these symptoms.

Quality of life and fatigue. The Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) (version 4) (Appendix I) is a quality of life (QoL) questionnaire developed to assess disease specific quality of life issues in patients with NHL (Cella et

al., 2005). It includes 27 questions covering the areas of physical, social/family, emotional and functional well-being (the same questions included in the core FACT/FACIT QoL questionnaire, the FACT-G), plus an additional 15 questions targeting NHL disease or treatment-related symptoms: With the exception of one question on concentration (*I have trouble concentrating*), cognitive functioning is not included in this questionnaire. The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale (version 4) (Appendix I) has 13 questions to assess symptoms of fatigue. The FACT questionnaires, including the FACT-Lym and FACIT-Fatigue scales, have shown good validity and reliability in cancer patients and have within-group responsiveness to change over time (Carter, Liepa, Zimmerman, & Morschhauser, 2008; Cella et al., 1993; Cella, Lai, Chang, Peterman, & Slavin, 2002; Cella et al., 2005; Downie, Mar Fan, Houédé-Tchen, Yi, & Tannock, 2006; Frank-Stromborg & Olsen, 2004).

Perceived (subjective) cognitive function. The Functional Assessment of Cancer Therapy-Cognitive (FACT-Cog) was developed to assess the nature, severity and impact of cognitive deficits in cancer patients: Validation of version 1 (Wagner, Sweet, Butt, Lai, & Cella, 2009; Lai et al., 2009), and version 2 (Jacobs, Jacobsen, Booth-Jones, Wagner, & Anasetti, 2007) have been reported. Jacobs et al. (2007) reported the FACT-Cog, v.2 demonstrated similar psychometric properties to the EORTC-CF (another commonly used measure of cognitive complaints) in hematopoetic stem cell transplant patients.

The FACT-Cog scale (version 3) (Appendix I) is a three page questionnaire with 37 questions that asks patients to rate their perceived cognitive functioning with the aim to

evaluate 'real-world' impact of chemotherapy-induced cognitive impairment (Rugo & Ahles, 2003; Tannock et al., 2004). The FACT-Cog questionnaire has been used in cancer- and chemotherapy-related cognitive impairment research studies to evaluate self-reported (perceived) cognitive function (Bénédicte et al., 2010; Jacobs et al., 2007; Lai et al., 2009; Rogers et al., 2008; Vardy et al., 2006, 2010; Wu et al., 2010). The FACT-Cog covers seven cognitive domains: Mental acuity, concentration, memory, verbal fluency, interference in functioning, other people noticing deficits, and change from previous function, as well as one quality of life domain (H. Morrow, personal communication, August 25, 2006). The 37 items on this questionnaire are divided into four subscales: 1) Perceived cognitive impairments (Cog-PCI) (20 items assessing mental acuity, concentration, memory, verbal fluency, interference in functioning, and multitasking); 2) impact of perceived cognitive impairments on quality of life (Cog-QOL) (4 items); 3) comments from others (Cog-OTH) (4 items); and 4) perceived cognitive abilities (Cog-PCA) (9 items assessing concentration, verbal fluency, memory, interference in functioning, mental acuity, and multitasking). The four items designed to assess multitasking (2 each in the perceived cognitive impairments and perceived cognitive abilities subscales) are currently not scored as per the FACT-Cog v.3 scoring guidelines (J. Bredle, personal communication, October 12, 2014; FACT/FACIT website), thus the scores for these 2 subscales are calculated on 18 and 7 items respectively. In contrast to the other FACT/FACIT questionnaires, the subscale scores are not added together to obtain a total score for the FACT-Cog (FACT-Cog v.3 scoring guideline).

Limited information on the psychometric properties of version 3 is available in the literature; however, this was the topic of an oral presentation at the October 2008

International Cognition and Cancer Task Force (ICCTF) workshop (Wagner, 2008). Despite the indication in the reference that a manuscript was in preparation, I have been unable to locate it on a literature search as recently as October 27, 2014. Wagner (2008) reports internal consistency as measured by Cronbach's alpha for Day 1 of cycle 4, and 6 months post chemotherapy respectively, was: 1) perceived cognitive impairment 0.95 and 0.94; 2) perceived cognitive abilities 0.73 and 0.67; 3) comments from others 0.75 and 0.90; and 4) impact of cognitive impairments on quality of life 0.89 and 0.92. Repeat administration of FACT-Cog, version 3, seven days post cycle 4, Day 1 assessment was reported as showing excellent test-retest reliability as measured by an inter-class co-efficient of 0.82 for the perceived cognitive impairment and perceived cognitive ability subscales, 0.79 for the comments from others subscale, and 0.86 for the quality of life subscale (Wagner, 2008).

All of the FACT questionnaires are Likert scales and are scored according to a manual provided by the publisher. Respondents are instructed to determine the frequency of occurrence of each symptom over the preceding seven days, with answers ranging from: 0 *(not at all),* 1 *(a little bit),* 2 *(somewhat),* 3 *(quite a bit),* 4 *(very much)* (FACT-Lym, FACIT-Fatigue, CogPCA and CogQOL on the FACT-Cog), or 0 *(never),* 1 *(about once a week),* 2 *(two to three times a week),* 3 *(nearly every day),* 4 *(several times a day)* for the CogPCI and CogOTH subscales on the FACT-Cog. The FACT questionnaires are self-administered, with the average time to completion 5 to 10 minutes and less for the stand-alone scales (i.e., FACIT-Fatigue) (Frank-Stromborg & Olsen, 2004; Functional Assessment of Chronic Illness Therapy (FACIT) website).

What amount of change in score on the PRO measures is clinically relevant? The concept of a minimally important difference (MID) or minimal clinically important difference (MCID) in health related quality of life measurement has been investigated for the FACT/FACIT questionnaires (Cheung et al., 2014; Hlubocky, Webster, Cashy, Beaumont, & Cella, 2013; Yost & Eton, 2005). MID has been defined as "the smallest difference in score in the domain of interest that patients perceive as important, either beneficial or harmful, and which would lead the clinician to consider a change in the patient's management" (Guyatt, Osoba, Wu, Wyrwich, & Norman, (2002), p.377). Yost and Eton (2005) report guidelines for calculating the MID on the FACT/FACIT scales based on a change in score of: 1) 0.15 - 0.25 points per item (4% - 6% of score) for Total scales; 2) 0.30 to 0.40 points per item (7%- 11% of score) for cancer specific subscales; and 3) 0.20 to 0.30 points per item (5% to 7% of score) for TOI (Trial Outcome Index). A difference of 0.15 to 0.26 points per item (3.7% to 6.5%) is reported as the MID for the FACIT-Fatigue subscale (Yost & Eton, 2005). Hlubocky et al. (2013) reported an estimated MID range for the Lyms (Lymphoma subscale) of 3 to 5 points or 5% to 8% of the scale range.

Cheung et al. (2014) have reported on the MCID for the FACT-Cog scale in breast cancer patients. Whilst the FACIT group advise against adding the subscales on the FACT-Cog to calculate a total score, these authors used the total score to estimate a range of 4.7% to 7.2% (6.9 to 10.6 points) as the MCID for this self-report questionnaire. For the purposes of this study, I divided the MCID point estimates by the number of items scored by Cheung et al. (a total of 37 items as they included the 4 multitasking items in the calculation of the total score) to yield an average of 0.19 to 0.29 points per item.

Whereas, the MID for the other FACT/FACIT scales can be used to determine either an improvement or deterioration in symptoms, Cheung et al. found that the MCID results for the FACT-Cog were only applicable to deterioration in perceived cognitive function (too few patients in their study demonstrated an improvement in cognition with an effect size of < 0.2).

Assessment of premorbid intelligence. Intelligence is a known predictor of neuropsychological test performance; however, as premorbid test data is rarely available, it is necessary to estimate an individual's premorbid cognitive ability (Kolb & Whishaw, 2009; Strauss, Sherman, & Spreen, 2006). Reading skills are relatively resistant to and independent of brain dysfunction (Schagen et al., 2008; Strauss et al., 2006). The National Adult Reading Test (NART) (including its various versions) was developed using irregularly spelled words that cannot be decoded phonologically and rely on previously acquired skills (e.g., ache, naïve, thyme) (Strauss et al., 2006). "The value of the test lies in (a) the high correlation between reading ability and intelligence in the normal population, [and] (b) the fact that word reading tends to produce a fairly accurate estimate of preinjury IQ …" (Strauss et al., 2006, p.190). It has been standardized to predict Weschler Adult Intelligence Scale – Revised (WAIS-R) IQ. All versions of the NART are reported to be "among the most reliable tests in clinical use" (Strauss et al., 2006, p.196), with internal consistency above 0.90, test-retest reliability of 0.92 to 0.98, inter-rater reliability of 0.99, and moderate to high correlations (0.40 - 0.80) with measures of general intellectual status (Strauss et al., 2006).

The NART has been modified for use in the North American population; the American National Adult Reading Test (AMNART) for use in the United States and the North American Adult Reading Test (NAART [61 words] and NAART35 [35 words]) for use in Canada and the United States (Strauss et al., 2006). Uttl (2002) reported the NAART35 was equally reliable and valid in predicting verbal intelligence when compared to the NAART. Scoring is based on the number of words pronounced correctly with equations provided for the calculation of the WAIS-R Vocabulary score (Strauss et al., 2006; Uttl, 2002). For the purposes of this study, the NAART35 (Appendix J) was administered at baseline (T1) only. Administration time was approximately 10 minutes.

Objective (neuropsychological) measurements. Assessment of cognitive functioning was conducted via standardized neuropsychological measures. Although the current knowledge on chemotherapy-related CD may not be sufficient to narrow down with certainty the affected domains for the purpose of assessment (Vardy, Wefel, Ahles, Tannock, & Schagen, 2008), it is generally agreed by researchers in the field that the deficits found on neuropsychological testing indicate dysfunction of the frontal and subcortical white matter networks (i.e. a frontal-subcortical profile) (Dietrich et al, 2008; Kean & Locke, 2008; Taillibert, Voillery, & Bernard-Marty, 2007; Vardy et al., 2008) and thus, the specific tests utilized need to be selected to ensure the cognitive domains most likely to be impacted (attention, processing speed, learning/memory functions, executive functions, and motor skills) are evaluated (Freeman & Broshek, 2002; Wefel, Kayl et al., 2004).

There are many valid and reliable tests available to assess cognitive function (American Academy of Neurology, 1996; Jansen, Miaskowski, Dodd, & Dowling, 2005; Strauss et al., 2006); however, most of these require a specially trained individual (neuropsychologist or psychometrist) for administration and interpretation (Strauss, Sherman & Spreen, 2006). A major disadvantage of the "gold-standard" neuropsychological tests is the length of time required for completion; usually a minimum of 2 ½ to 3 hours to complete the battery of tests at each testing time-point (Jansen, Miaskowski, Dodd, & Dowling, 2005; Rugo & Ahles, 2003) and up to four to seven hours to conduct a full cognitive assessment (Myers, 2009). Participant burden must be considered when selecting the tests to use: Patients may have disease related symptoms or treatment related side effects that may limit their ability and/or willingness to complete lengthy evaluations (Jansen, Miaskowski, Dodd, & Dowling, 2005). Another potential issue is the effect of practice or learning on performance, making it difficult to know if improvement is simply due to practice effects or is a true observation (Nail, 2006; Wesnes, & Pincock, 2002).

In 2011 the International Cognition and Cancer Task Force (ICCTF) published recommendations for a core set of neuropsychological tests to be considered for use in research studies investigating cognitive changes associated with non-CNS cancer (Wefel, Vardy, Ahles, & Schagen, 2011). The tests selected included the Hopkins Verbal Learning Test – Revised (HVLT-R), Trait Making Test (TMT), and the Controlled Oral Word Association (COWA) of the Multilingual Aphasia Examination. Learning and memory, processing speed and executive function are the cognitive domains measured by these tests. The authors also advise incorporating tests of working memory to the core battery,

with the specific tests left to the investigator's preference. It must be noted that these guidelines were published after the design and initiation of the current research study.

In this study, I used the CogState Academic, a computerized battery of cognitive tests developed for the purpose of measuring change in cognition in situations where repeated assessment of individuals is required (CogState website; Falleti et al., 2006). The tasks included in the test battery can be customized as appropriate for each study. The cognitive domains that can be assessed by the CogState battery include: visual motor function, psychomotor function/processing speed, visual attention/vigilance, visual learning and memory, attention/working memory, verbal memory, executive function, and social cognition (CogState website; Maruff et al., 2009). The CogState battery has been shown to have good validity, strong test-retest reliability, high stability and sensitivity and is reported to be capable of detecting subtle changes in cognitive function (CogState website; Darby, Maruff, Collie, & McStephen, 2002; Fredrickson et al., 2010).

A total of 13 separate tasks were chosen from the CogState neuropsychological test battery to be administered to the subjects in this study. These tasks were chosen as they include the cognitive domains previous research has identified as potentially impacted in cancer patients receiving chemotherapy. The cognitive function tested and the primary outcome measure(s) for each of these tasks is documented in Table 1. In addition, see Appendix K for a detailed description of the CogState Academic battery tasks used in this study.

Table 1

Description of CogState tasks

Task	Task Name	Cognitive Function Tested	[a]Primary Outcome Measure
DET	Detection	Psychomotor function	lmn
IDN	Identification	Attention	lmn
GMCT	Groton maze timed chase test	Speed of visual processing	mps
GML	Groton maze learning test	Executive function	ter
GMR	Groton maze learning test – delayed recall	Delayed recall	ter
ISL	International shopping list	Verbal learning	cor
ISLR	International shopping list – recall	Verbal learning – delayed recall	cor
OCL	One card learning	Learning	acc
ONB	One back memory	Working memory - simple	acc; lmn
TWOB	Two back memory	Working memory - complex	acc; lmn
CPAL	Continuous paired associate learning	Paired associate learning	err
SETS	Set shifting	Executive function	err
SECT	Social emotional cognition task	Social emotional cognition	acc

[a] lmn – speed measure; mps – speed and accuracy measure; ter, cor, acc and err – accuracy measures. See chapter 4 for a more detailed description of the interpretation and scoring of the primary outcome measures for each task

The CogState battery has been tested and used in a variety of different conditions, including, among others: Sports-related concussion, traumatic brain injury, coronary surgery, HIV/AIDS, MCI, fatigue, neuroepidemiological studies in the elderly (CogState

website; Falleti, Maruff, Collie, & Darby, 2005, 2006; Fredrickson et al., 2010; Pietrazak, Maruff, & Snyder, 2009), and in breast cancer patients on chemotherapy (Boivin et al., 2008; Darby, Falleti, Maruff, & Phillips, 2008; Falleti, Maruff, & Phillips, 2007; Vardy et al., 2006).

The extensive version of the CogState battery was completed by the participant on a laptop computer, taking approximately 60 minutes to complete. There is a practice session for each task prior to the subject competing the actual test, thus the time spent by the participant to complete the test battery included this practice time. The data from each of the tests are automatically uploaded to an online data management system (DataPoint®) at CogState for ongoing data discrepancy management, as well as allowing immediate review of the data that was sent on the same day of testing. Scores are provided for each of the tests administered and are available for each of the cognitive domains assessed by the test battery.

Blood samples for banking for future research. Cognitive dysfunction does not occur in all cancer patients who have received chemotherapy, instead having been documented in only a subgroup of these patients. One of the reasons for this variation that has been suggested is that biological factors may place vulnerable individuals at greater risk of developing CD (Ahles & Saykin, 2007; Wefel et al, 2008). Examples of potential contributing biomarkers that have been identified include: 1) polymorphisms in neural plasticity and repair genes (e.g., APOE, brain-derived neutrophic factor [BDNF]); 2) polymorphisms in efflux transporter proteins (e.g., multidrug resistance 1 (MDR1) gene, organic anion-transporting polypeptide-A [OATP-A]); 3) polymorphisms in genes that

modulate metabolism of neurotransmitters (eg., catechol-o-methyl-transferase [COMT]); and 4) polymorphisms in genes regulating the folate pathway (Ahles et al, 2003; Ahles & Saykin, 2007; Egan et al., 2003; Love et al., 2006; McAllister et al., 2004; Wefel et al., 2008). More recently, clusterin, an extracellular chaperone protein that regulates the formation and removal of amyloid, has been reported to be associated with the development, severity and progression of Alzheimer's disease (Thambisetty et al., 2010).

Testing of banked samples linked to a clinical database is potentially useful in facilitating an understanding of biological and genetic mechanisms including the determination of predictive factors that may contribute to the development of treatment related toxicities.

The original intent was to ask patients if they were willing to provide consent for the collection of blood samples at baseline and 1 month following completion of chemotherapy for banking for future research purposes. Thus a "Banking for Future Research" consent form was developed and submitted to the REB for approval (attached in Appendix F). Unfortunately, by the time the study was open for enrollment, organizational changes (switch from Alberta Cancer Board to Alberta Health Services) and changes to laboratory billing for samples collected for research purposes, resulted in an inability to collect, process and store these samples due to the absence of funding to pay these charges.

Data collection schedule. Data collection took place when the patients were seen in the OPD clinic for their regularly scheduled appointment the day prior to their planned chemotherapy. The day of chemotherapy was not used to administer the test instruments

for this study, as patients were given pre-medications (steroids, diphenhydramine) that may have affected their performance on the tests. A quiet, private room was used for the testing procedures. If another time was more convenient for the patient this was arranged, as long as the testing took place prior to the administration of the chemotherapy treatment.

Data were collected by myself or a trained research assistant at the following intervals:

1. Baseline prior to start of chemotherapy (T1)
    - demographic and disease related information,
    - self-administered standardized questionnaires on anxiety, depression, stress, fatigue, quality of life, subjective cognitive functioning,
    - assessment of premorbid intelligence,
    - standardized neuropsychological testing to measure cognitive function.
2. During chemotherapy (after cycle 3 or cycle 4, or for those receiving 3 cycles and IFRT, after cycle 3 and prior to the start of RT) (T2)
    - disease and treatment related information,
    - self-administered standardized questionnaires on anxiety, depression, stress, fatigue, quality of life, subjective cognitive functioning,
    - standardized neuropsychological testing to measure cognitive function.

3. At approximately 1 month (T3), 6 months (T4), and 1 year (T5) following completion of chemotherapy (or IFRT for those subjects receiving 3 cycles and RT)
    - disease and treatment related information,
    - self-administered standardized questionnaires on anxiety, depression, stress, fatigue, quality of life, subjective cognitive functioning,
    - standardized neuropsychological testing to measure cognitive function.

Duration of Study Recruitment

It took 3 years to reach the target study sample of 100 subjects.

Duration of Patient Participation

As the data collection included the treatment period and several points over the year following completion of treatment, the duration of patient participation in this study was approximately 1 ½ years.

Data Analyses

The data obtained from the questionnaires and the neuropsychological tests were interval data. Results were scored and entered into the appropriate computerized statistical software program(s) (e.g., SPSS, SAS) as per the instruction manual(s) of the publisher(s) of the instruments. The nominal data (e.g., sex, level of education, type of lymphoma, chemotherapy regimen, etc.) were coded for entry into the statistical software program. Dates (date of birth, date of diagnosis, etc.) were entered. All of the data were double

checked by the researcher for accuracy both prior to and following entry into the software program.

Data analyses were conducted using the computerized statistical software program IBM SPSS Statistics (version 22.0) or SAS (SAS Institute Inc., Cary, NC) (version 9.3) as appropriate. The significance level was set at $p < 0.05$. Two-tailed tests were planned as it was impossible to know in advance if the effect would be directional. Although the intent of the study was to determine if cognitive deficits develop or worsen with chemotherapy (negative effect), it was possible an improvement (positive effect) might be seen.

When the sample size is large (> 30), the central limit theorem applies and parametric statistical tests can be used (Daniel, 2005). Descriptive statistics were obtained, including frequencies, paired t-tests, generalized estimating equation (GEE) and correlation coefficient (e.g., Pearson's *r*). Paired t-tests were used to compare results when the data were from the same subjects (*within*-subject) at two time-points (Polit & Beck, 2004).

Research question 1: What are the manifestations of cognitive dysfunction/impairment over time in non-Hodgkin's lymphoma patients receiving front-line chemotherapy at the Cross Cancer Institute? Generalized estimating equations (GEE) (Liang & Zeger, 1986) are appropriate for analyzing repeated measures data in longitudinal studies and for "analyzing the relationship between dependent variables and one or more predictor variables over time" (Liu, Dixon, Qiu, Tian, & McCorkle, 2009, p.949). The classical regression methods (e.g., ANOVA) assume that the observations in the data are independent; however, in the case of repeated measurements

in the same individual there is a lack of independence in a participant's responses across time (i.e., the correlation between any two scores for the same variable for any one participant is assumed to be constant [compound symmetry]) (Hann, Semanski, Jagust, Manolio, & Kuller, 1999). The accuracy and validity of the results can be compromised when statistical methods that do not take this correlation into account are used (Liu et al, 2009). GEE provides a method for handling the correlations of repeated measurements of variables, providing robust and consistent standard errors (Liang & Zeger, 1986). Additionally, in the case of missing data (a common problem in longitudinal studies), GEE permits the inclusion of all available data from all subjects (regardless of whether there is a complete data set on the subject or not) to be included in the analysis and 'missingness' is assumed to be completely at random, thus avoiding the exclusion of those subjects (and all of their available data) who have not provided responses at all time-points (Liu et al., 2009).

Research question 2: What factors predict cognitive dysfunction/impairment experienced by non-Hodgkin's lymphoma patients receiving front-line chemotherapy at the Cross Cancer Institute? The correlation coefficient summarizes the magnitude and direction of a relationship between variables measured on an interval scale, and can be used in *within*-group and *between*-group situations (Polit & Beck, 2004). Correlation coefficient statistics were used to examine relationships among the variables of age, education, hemoglobin level, depression, fatigue, anxiety, stress, and each of the cognitive function measures obtained on the tasks in the CogState test battery. In order to determine the potential factors contributing to cognitive dysfunction at each time-point, separate regression equations for each cognitive function measure were developed, with the

cognitive function measure as the dependent variable, and the study variables (age, education, depression, fatigue, anxiety, and stress) that had correlations of +/- 0.3 with the cognitive function measure being tested as the independent variables. As the cognitive function is measured as a continuous variable, a linear regression approach was used.

Research question 3: Is there a correlation between objective (neuropsychological) and subjective (perceived) cognitive assessments in non-Hodgkin's lymphoma patients receiving front-line chemotherapy at the Cross Cancer Institute? Pearson's *r* was used to examine correlations between measures of each cognitive domain on the objective and subjective cognitive tests.

Research question 4: Is there a correlation between cognitive dysfunction/ impairment and quality of life in non-Hodgkin's lymphoma patients receiving front-line chemotherapy at the Cross Cancer Institute? Pearson's *r* was used to examine correlations between measures of each cognitive domain on the objective tests and patient reported quality of life.

Ethical Considerations

This research proposal was submitted to the Alberta Cancer Research Ethics Committee (ACREC) and the University of Alberta Health Research Ethics Board (HREB) Panel B for approval. Following receipt of the letters of approval from both REBs (attached in Appendix E), accrual to the study commenced. Written informed consent was obtained from the study participants prior to any study procedures being initiated. Participation in the study was voluntary and participants were able to withdraw

from the study at any time if they so desired. A decision not to participate in the study and/or to withdraw from the study had no effect on a participant's ongoing medical care.

Free and informed consent is the central ethical issue which must be considered in individuals who may be at risk of CD and diminished decision making capacity (DMC): Every effort must be made to ensure the potential study subject has an accurate understanding of the proposed research prior to making the decision to participate. The informed consent process does not occur on only one occasion, but is an ongoing process. In the case of chemotherapy related CD, the deficits are generally subtle, with cognitive function often within the normal range (Ahles et al., 2002; Ahles et al., 2003; Schagen et al., 1999; van Dam et al., 1998), therefore these patients would not be considered incapable of making an informed decision, however, because of the nature of the deficits they may be experiencing (e.g., reduced attention and concentration, memory problems), the informed consent process may be more involved and take more time than it would for someone without CD. This should include taking time to clarify with potential participants their understanding of the research, the trial-specific procedures, potential benefits and risks, and the differences between research and standard care (Erlen, 2000). Discussion of this study did not require any additional or extraordinary measures different from the approach involved when discussing either standard (i.e., non-study) therapy or other clinical trial options with this patient population.

Participant confidentiality was maintained by assigning each subject a unique study identification number. No identifying demographic information was included on the questionnaires or the neuropsychological test results (paper and/or computerized tests).

The researcher was the only individual to have access to the identities of the participants. The data collected were and continue to be maintained in a locked cabinet at the Cross Cancer Institute when not in use. A copy of the signed consent was provided to the participant and the original is being kept in a locked cabinet separate from the cabinet where the study data are kept.

There were no potential risks anticipated as a result of participation in the study. Regardless of their participation in this study, all patients were advised by their hematologist/medical oncologist to take chemotherapy as treatment for their lymphoma. As these patients had not previously been offered or received chemotherapy, I had no prior contact with them in my position as Nurse Practitioner at the CCI; therefore, there was no potential conflict in approaching the patients directly. In the majority of cases, the hematologist/medical oncologist seeing the patient introduced the study concept to the potential participant before I met with him/her.

Chapter 4: Results

A total of 110 subjects with lymphoma scheduled to receive chemotherapy with or without involved field radiation (IFRT) provided written signed consent and were enrolled into the study between November 2010 and February 2014. However, eight of the subjects who signed consent withdrew prior to the T1 assessment and an additional two subjects withdrew consent after starting but before completing baseline testing; thus, baseline (T1) data are available on 100 subjects. Reasons provided for withdrawal of consent included: no reason given (2); did not keep appointment and did not respond to follow-up phone call (1); researcher's unanticipated absence which resulted in an inability to obtain baseline testing (1); refusal to complete the computerized neurocognitive testing (1); increased stress and anxiety (5).

Potentially eligible subjects were identified via a number of different approaches: The researcher's attendance at weekly lymphoma rounds where all new patients are reviewed; periodic reminders of the availability of the study to the medical and nursing staff in the lymphoma tumour group; the researcher's attendance at the various outpatient (OPD) lymphoma clinics; referrals from members of the hematology tumour group (physicians, OPD nurses, clinical research nurses).

Whilst not every patient who was considered for the study was recorded on a screening log, some of the reasons for ineligibility were: Poor performance status; indolent lymphoma on a wait and watch policy (i.e., no treatment); diagnosis of Hodgkin's lymphoma; previous cancers with treatment within the preceding five years; planned upfront high dose chemotherapy and hematopoietic stem cell transplant (HSCT); inability

to speak English; chemotherapy administered at one of the community cancer centres in Alberta (i.e., geographically distant) with no plans for regular review at Cross Cancer Institute; diagnosis of mild cognitive impairment (MCI); diagnosis of HIV; history of psychiatric illness, not well controlled; commenced on chemotherapy immediately after being seen with no opportunity to obtain baseline testing.

Of those patients who were approached but declined participation, a number gave no reason for their decision. In a few cases the patient was interested, however the family member(s) were not supportive/did not want them to take part and thus the patient deferred to the family's wishes. Other reasons given were that it was too stressful, they were too anxious, unable to stay to complete the testing, the testing would take too much time, feeling too unwell.

The study results/data presented in this report include follow-up collected up to September 24, 2014. At that time all subjects had completed their planned chemotherapy. As of September 24, 2014, the number of subjects completing each assessment time-point were: Baseline (T1) – 100; midway through planned treatment (T2) – 94; at end of planned treatment (T3) – 90; first follow-up (T4) – 63; second follow-up (T5) – 48. Twenty-eight subjects discontinued from the study prior to completing all five of the planned assessments. See Figure 1 "Disposition of Subjects at Various Time-points" for details.

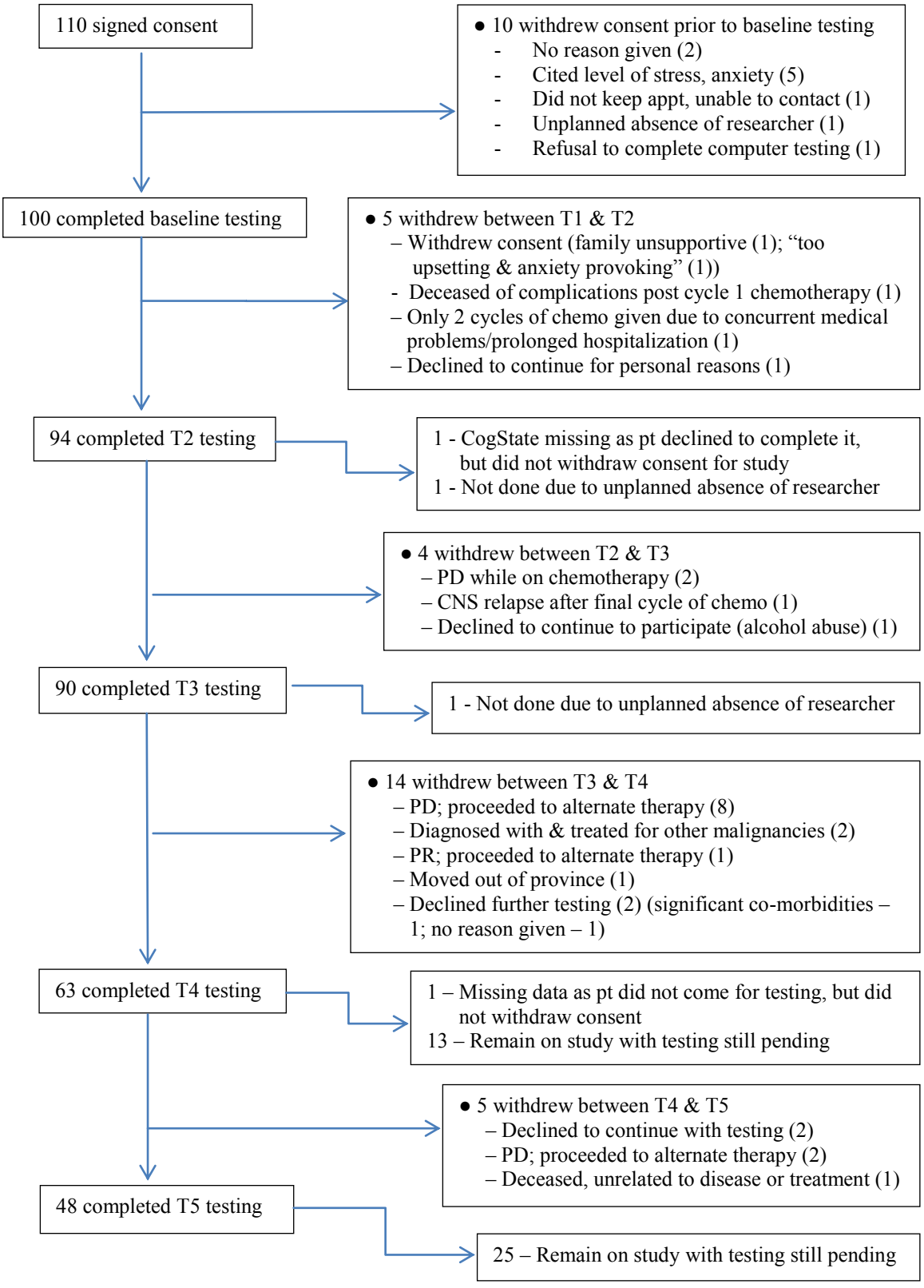

Figure 1. Disposition of Subjects at the Various Time-Points. PD = Progressive Disease; CNS = Central Nervous System; PR = Partial Response. Information current as of September 24, 2014

This report will focus on the results of the first three assessment time-points, as a significant number of subjects (n = 38) remain on study with follow-up testing still pending. The complete study results will be analyzed, reported and published when the remaining subjects have completed all testing time-points, anticipated to be summer 2015.

Subject Characteristics

The study sample of 100 subjects consisted of 65 males and 35 females. Age range at time of diagnosis was 26 – 88 years with a mean of 61 years and standard deviation (SD) of 10.7 years (Table 2). This is consistent with the published age and sex distribution of patients diagnosed with NHL in Alberta as shown in the graph below (Alberta Health Services, 2010, p.11).

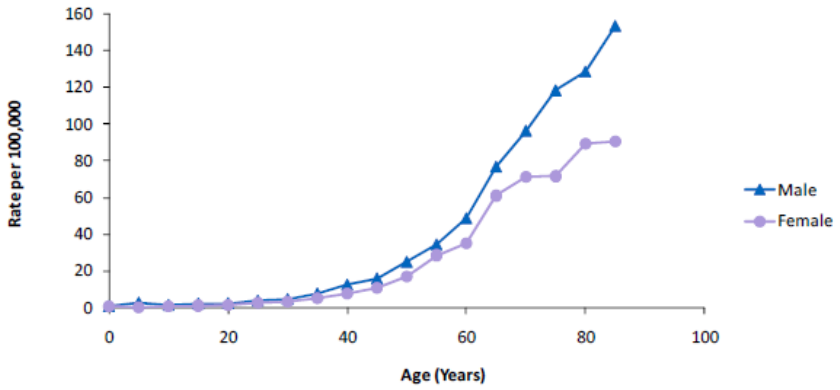

Figure 2. Age-specific incidence rates for non-Hodgkin's lymphoma by sex, Alberta, 2004-2008. Source: Alberta Health Services, 2010, p.11.

The age at study enrollment was essentially the same as at diagnosis as can be seen in Table 2. As per standard practice, some patients with indolent lymphoma who were asymptomatic at time of diagnosis were followed on a wait and watch policy until they developed symptoms that required initiation of therapy. Thus, for some individuals the age

at date of diagnosis is not the same as at time of study enrollment. The longest time between diagnosis and study entry was 13 years.

The majority of subjects self-reported as Caucasian (97%) with 3% being of Aboriginal/Metis ethnicity. The majority (86%) (30/35) of the female subjects reported they were post-menopausal. The study cohort was highly educated with 80% having 12 years or more of formal education and 43% having postsecondary education. The majority were right handed. The demographics were evenly matched between men and women with the exception of education, with 85% of women having ≥ 12 years of education compared to 77% of men. See Table 2 for details of demographic data.

Table 2

Demographic Data

Characteristic	Total N = 100	Male n = 65	Female n = 35
Gender:			
Male	65		
Female	35		
Age (years):			
At Diagnosis:			
Range	26 – 88	26 – 88	40 – 82
Median	62.3	63.1	59.78
Mean	61	60.98	61.4
At Study Entry:			
Range	26 - 88	26 - 88	40 - 82
Median	62.4	63.1	59.97
Mean	61.8	61.6	62.3
Ethnicity:			
Caucasian	97	64	33
Aboriginal/Metis	3	1	2
Postmenopausal:	30/35	--	30 (85.7%)
Highest Level of Education:			
Grades 7, 8, 9	8	6	2
Grades 10, 11	12	9	3
Grade 12	37	22	15
College	21	12	9
University:			
Bachelor degree	13	8	5
Graduate degree	7	6	1
Partial	2	2	2
Education by Years Completed:			
< 12 years	20	15	5
12 – 15 years	59	36	23
16 years	12	7	5
>16 years	9	7	2
Handedness: Right	89	58	31

Disease Characteristics

Non-Hodgkin's lymphoma is not just one disease, but is comprised of over 50 different subtypes (Swerdlow, et al., 2008). The specific histologies of the subjects enrolled in this study are: Large B-cell lymphoma (diffuse large B-cell lymphoma (DLBCL) (n = 50) and primary mediastinal large B-cell lymphoma (n = 2)); follicular lymphoma (FL), grade 1, 2, or 3a/3 (n = 31); mantle cell lymphoma (MCL) (n = 4); Waldenström's macroglobinemia/lymphoplasmacytic lymphoma (WM/LPL) (n = 5); chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (n = 2); mucosal associated lymphoid tissue (MALT) (n = 2); marginal zone lymphoma (MZL) (n = 1); plasmablastic large cell lymphoma (CD20 neg.) (n = 1); ALK1+ anaplastic large T-cell lymphoma (n =1); CD20+ lymphocyte predominate Hodgkin's lymphoma (n = 1). Aggressive subtypes were diagnosed in 58% of subjects compared to 42% with indolent (less aggressive) histology. This is consistent with the frequency of diagnosis of the various lymphoma subtypes as published in the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (Swerdlow et al., 2008, p. 164-165).

Just over two-thirds (68%) of subjects had advanced disease (stage 3 or 4) (males 63%; females 77%). Stage 1 disease was present in 17% (males 18.5%; females 14.2%); stage 2 disease in 15 % (males 18.5%; females 8.6%).

The majority of subjects either had no or minimal symptoms affecting daily functioning as measured by ECOG performance status (PS) of 0 or 1 (81%), with PS of 2 in 16% and PS of 3 in 3% (see Appendix D for details of ECOG PS criteria). Slightly more men had no symptoms (PS of 0) (44.6%) than women (37%), whilst more women

(46%) than men (35.4%) were PS of 1. However, when combining these 2 PS levels, there were no differences between males and females (80% and 83% respectively). At the time of initial consultation by the medical oncologist, three males (4.6%) were experiencing significant symptoms (PS of 3), however once they had received supportive care interventions (e.g. correction of hypercalcemia, adequate analgesia, anti-emetics, etc.) performance status had improved to a level of 2 and they were considered to be eligible for inclusion into this study. B symptoms, defined as one or more of drenching night sweats, unintended weight loss of > 10% in the previous 6 months, and/or unexplained fevers > 38^{o}C, were reported by 27% of subjects. These symptoms are generally thought of as representing more aggressive disease regardless of histology or stage, however are not included in any of the prognostic indices used to categorize an individual's risk status. Details of disease characteristics are presented in Table 3.

Table 3

Disease Characteristics

Characteristic	Total N = 100	Male n = 65 (%)	Female n = 35 (%)
[a]**Diagnosis:**			
Large B cell lymphoma			
DLBCL	50	34 (52.3)	16 (45.7)
Primary mediastinal	2	0	2 (5.7)
FL	31	20 (30.7)	11 (31.4)
MCL	4	3 (4.6)	1 (2.9)
WM/LPL	5	4 (6.2)	1 (2.9)
Other	8	4 (6.2)	4 (11.4)
Stage:			
1	17	12 (18.5)	5 (14.2)
2	15	12 (18.5)	3 (8.6)
3	26	16 (24.6)	10 (28.6)
4	42	25 (38.4)	17 (48.6)
B symptoms: Yes	27	18 (27.6)	9 (25.7)
[b]**ECOG PS**			
0	42	29 (44.6)	13 (37)
1	39	23 (35.4)	16 (46)
2	16	10 (15.4)	6 (17)
3	3	3 (4.6)	0

[a]DLBCL – diffuse large B cell lymphoma; FL = follicular lymphoma; MCL = mantle cell lymphoma; WM/LPL – Waldenstrom macroglobinemia/lymphoplasmacytic lymphoma; Other – chronic lymphocytic leukemia/small lymphocytic lymphoma (2), mucosal associated lymphoid tissue (2), marginal zone lymphoma (1), plasmablastic large cell lymphoma (1), Alk1+ anaplastic large T cell (1), CD20+ Hodgkin's lymphoma lymphocyte predominant (1).
[b]See Appendix D for details

Treatment Specifics

The vast majority of subjects (98%) received a CD20+ monoclonal antibody (MAb) in addition to chemotherapy as is standard practice for CD20+ lymphoma. Patients were treated with either rituximab (R) (the standard CD20 MAb) or GA101 (G). GA101 (obinutuzumab) is an investigational CD20 MAb which at the time of recruitment into this study was available as part of two separate phase 3 clinical trials: 1) one for DLBCL; and 2) one for FL. These were RCTs where patients were randomized to receive either rituximab or GA101 in addition to chemotherapy. Thus, for DLBCL, patients were assigned to either R-CHOP or G-CHOP, and for FL, patients were assigned to R-Bendamustine or G-Bendamustine.

Sixty subjects were treated with CHOP or a CHOP-like regimen plus a MAb (R-CHOP [n = 52]; G-CHOP [n = 6]; R-CEOP [n =2]). In the R-CEOP regimen, the doxorubicin was replaced by etoposide because of concerns regarding potential cardiotoxicity with doxorubicin.

For patients who were not eligible for treatment on the Phase 3 RCT, the standard therapy for indolent lymphoma at the start of this study was R-CVP. R-CVP was then phased out early in 2013 when Bendamustine plus rituximab was adopted as the standard chemotherapy in Alberta for this histologic subtype. Thus, only 8 subjects were treated with R-CVP prior to the switch being made to Bendamustine (Benda). Twenty-nine subjects received Bendamustine plus a MAb (R-Benda [n = 23]; G-Benda [n = 6]). Two subjects were treated with CHOP only (the individual with the T-cell lymphoma and the subject with the CD20 negative plasmablastic large cell lymphoma). (CD20 MAbs are

effective and indicated only if the patient's lymphoma cells express CD20). One subject with DLBCL received more intensive chemotherapy (R-CODOX-M) as his disease was considered higher risk ("double-hit" with both Bcl-6 and c-myc testing positive). Intrathecal chemotherapy was not administered in this subject's case as there was no evidence of CNS involvement. Please refer to footnote at bottom of Table 4 for details of the specific drugs included in each regimen.

R-CHOP, R-CEOP, G-CHOP, R-CVP are all administered on a 3 week cycle, R(G)-Bendamustine is given on a 4 week cycle, and the R-CODOX-M is a more intensive regimen with the treatment cycles administered every 2 - 3 weeks. With the exception of R-CODOX-M which requires the patient to be admitted to the inpatient unit for the duration of the treatment, all of the other regimens are given on an outpatient basis in the medical daycare unit.

The number of cycles of chemotherapy subjects received ranged from 1 – 8, with a median of 6 and a mean of 5.54 (males 5.57; females 5.48). One subject deceased after 1 cycle of chemotherapy due to complications of treatment. One subject received 2 cycles of chemotherapy which was then discontinued due to prolonged hospitalization for concurrent medical problems and general poor health. Of the 14 subjects who received 3 cycles of chemotherapy, this was preplanned in 13 as is standard for limited stage disease. Eleven of these were treated with preplanned IFRT as consolidation following completion of the third cycle of chemotherapy. Three patients received only the 3 cycles of chemotherapy (i.e., without IFRT): 1) subject with disease confined to the spleen at diagnosis and who had undergone splenectomy prior to chemotherapy; 2) the subject with the higher risk disease who received the intensive R-CODOX-M regimen; and 3) one

subject who had the chemotherapy discontinued after 3 cycles after developing pulmonary toxicity.

An additional 12 subjects received preplanned IFRT after completion of 6 cycles of chemotherapy as is standard practice for bulky disease, localized aggressive lymphoma, or with involvement at higher risk sites (e.g., testicle, localized bone involvement).

Relapsed or progressive lymphoma was diagnosed in a total of 17 subjects (11 males, 6 females) as of September 24, 2014, with 16 subjects (10 males, 6 females) deceased as of the same date. The cause of death in 14/16 was progressive/relapsed lymphoma. In the other two cases, one subject died of heart failure and cardiopulmonary arrest after one cycle of chemotherapy, whereas in the other case the cause of death was not cancer or treatment related (sepsis/ARDS one year after completion of chemotherapy).

A second primary malignancy (colorectal cancer) was diagnosed in 2 male subjects. They were treated with the appropriate therapy (chemotherapy +/- radiotherapy) for the new malignancy. These subjects were discontinued from the study as the additional therapy would have made it difficult to interpret the study test results.

Table 4

Treatment Characteristics

Characteristic	Total N = 100	Male n = 65 (%)	Female n = 35 (%)
[a]**Chemotherapy Regimen:**			
R-CHOP	52	32 (49.2)	20 (57.1)
R-CVP	8	5 (7.7)	3 (4.6)
R-Benda	23	13 (20)	10 (28.6)
G-Benda	6	6 (9.2)	0 (0)
G-CHOP	6	4 (6.2)	2 (5.7)
Other	5	5 (7.7)	0 (0)
[b]**IFRT:** Yes	23/100	17 (26)	6 (17)
3 cycles of chemo + IFRT	11/23	10 (15)	1 (2.8)
# of cycles of chemo:			
1	1	0 (0)	1 (2.9)
2	1	0 (0)	1 (2.9)
3	14	11(16.9)	3 (8.6)
5	3	1 (1.5)	2 (5.7)
6	77	50 (77)	27 (77)
8	4	3 (4.6)	1 (2.9)
Median	6	6	6
Mean	5.54	5.57	5.48
Disease Progression: Yes	17	11 (17)	6 (17)
Death: Yes	16	10 (15.4)	6 (17)

[a]R=CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone); R-CVP (rituximab, cyclophosphamide, vincristine, prednisone); R-Benda (rituximab, bendamustine); G-Benda (GA101-Bendamustine); G-CHOP (GA101, cyclophosphamide, doxorubicin, vincristine, prednisone); Other – CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) (2), R-CEOP (rituximab, cyclophosphamide, etoposide, vincristine, prednisone) (2); R-CODOX-M (rituximab, cyclophosphamide, vincristine, doxorubicin, methotrexate) (1)
[b]IFRT = Involved field radiation therapy

Data Analysis

Subject completion of testing.

The number of subjects completing testing at each time-point is indicated in Table 5.

Table 5

Number of Assessment Time-points Completed by Number of Subjects

n	T1	T2	T3
89	√	√	√
5	√	√	X
1	√	X	√
5	√	X	X
Total	100	94	90

There are missing data on 4 of the subjects recorded as having completed all 3 time-points: 1) only PRO measures are available on two subjects at T3 (1 subject with symptomatic progressive disease who did not feel up to completing the computerized testing, and 1 subject who refused to complete the computerized testing); 2) only PRO measures are available on one subject at T2 and T3 due to subject refusal to complete the computerized testing; 3) PRO measures and partial computerized testing at T3 in one subject due to disease related symptoms (abdominal pain and vomiting, which precluded completion of the CogState battery); 4) one subject refused to complete the NAART testing at T1 (same subject who refused computerized testing at T3 in point # 1 above).

NAART35.

The North American Adult Reading Test 35 (NAART35) was administered at T1 only. It is scored on the number of words pronounced correctly out of 35. The reliability and validity results of the NAART/NAART35 have been published (Strauss et al., 2006; Uttl, 2002) and are discussed in Chapter 3, pages 44 - 45. The age and education norms

will be discussed below in relationship to the results obtained in the analysis of the current study.

A total of 99 subjects completed the NAART35 at baseline, with one subject declining. The results are comparable between males and females, which is consistent with the published reports that gender has no or minimal effect on performance scores (Uttl, 2002). Uttl (2002) reports a moderate increase in NAART scores by approximately 4.5 points (0.5 SD) across the adult life span based on the 3 age categories of: 1) young (18 - 39), 2) middle aged (40 - 59), and 3) older (60 – 91); and by approximately 1.5 points for each year of education. See Tables 6 and 7 for results by gender and by years of education (all results are scored out of a maximum of 35). As shown in Table 7, there was an increase in both the mean and median score with increasing years of education with analysis of variance (ANOVA) statistically significant with a p value of <0.001.

Table 6

NAART35 Mean, Median and Range

NAART35	Males n = 65	Females n = 34
Mean	24.30	24.29
Median	24	23.5
Range	12 - 34	15-34

Table 7

NAART35 Scores by Years of Education

Years of education	n	NAART35 Scores			
		M	SD	Range	Mdn
<12 Years	19	20.53	4.46	12 - 28	20
12-15 years	59	24.25	4.61	15 - 34	23
16 years	12	26.92	3.63	21 - 32	28
>16 years	9	29.11	3.86	24 -34	30
Total	99	24.30	4.96	12 -34	24

Note. M = mean; SD = standard deviation; Mdn = median

Uttl (2002) reports age norms by 10 year cohorts (25-35; 35-45; … 75-91) for all participants, as well as providing normative data based on education levels (≤ 15years; ≥ 16 years) for each of the age cohorts. For the purposes of placing my study participants into 10 year age cohorts, I divided the age ranges as follows: 25 - 34, 35 - 44, 45 - 54, 55 - 64, 65 - 75, and 75 - 91. ANOVA on these age cohorts and the 2 educational levels was not statistically significant ($p = 0.443$). With the exception of the youngest cohort (25 – 34 years) with a mean score of 29, the mean scores for the other cohorts are more or less the same as reported by Uttl (2002, p. 1133). There are only 2 subjects in the 25 – 34 year cohort in the current study and as such it is impossible to compare to the published norms (mean 21.39; SD 6.32) for that age group, although if one were to take the scores in the upper range of the published SD, this would be approximately equivalent to the results for the 2 subjects in the youngest age cohort. Similar to the findings reported by Uttl, as can be seen in Table 8, the mean score improved with increasing age (excluding the youngest

cohort). However, when the analysis was run on the 2 age groups of middle aged (40 – 59 years) and older adults (60 – 91 years), there was no difference (mean 23.2 (SD 4.8) vs 25.04 (4.99) and median 23 vs 25 respectively).

Table 8

NAART35 Results Based on Age Cohorts and 2 Levels of Education

		Age Group (at time of consent/entry into study)					
		25-34	35-44	45-54	55-64	65-74	75-91
All subjects	n	2	5	15	35	33	9
	M	29	21.80	22.80	24.57	24.61	25.00
	SD	(1.41)	(6.42)	(3.60)	(5.44)	(4.81)	(5.05)
By Years of Education							
≤ 15 years	n	1	4	13	26	27	7
	M	28	20.50	22.31	23.38	23.85	24.14
	SD		(6.60)	(3.40)	(5.25)	(4.82)	(4.98)
≥ 16 years	n	1	1	2	9	6	2
	M	30	27	26	28	28	28
	SD			(4.24)	(4.66)	(3.23)	(5.66)

Note. n = number of subjects; M = mean; SD = standard deviation

DASS21.

The Depression/Anxiety/Stress Scale 21 (DASS21) consists of a total of 21 questions, with 7 items for each of the 3 subscales (depression, anxiety, and stress). The items are answered on a 4 point Likert scale with a maximum score of 28 per subscale. In order to calculate the severity of the symptom, the total subscale score is multiplied by 2

to make it comparable to the full DASS questionnaire which has 14 items per subscale. Thus, the range of scores for each of the depression, anxiety, and stress subscales is 0 (no symptoms) to 56 (extremely symptomatic). A higher score indicates more symptoms, which is the opposite of the FACT/FACIT scoring where a higher score indicates fewer symptoms. A total of 99 participants completed the DASS21 at T1 (one questionnaire was missing and could not be located), 94 at T2, and 90 at T3.

In the event items on the self-report questionnaires were not answered and left blank, the missing data has been dealt with as per the recommendations of the publishers of the specific scales. The publisher of the DASS21 recommends a limit of no more than 1 missing item per 7 item subscale with averaging over the remaining items for that scale considered acceptable (DASS website). Therefore, if there was only 1 item missing on a scale (i.e., depression, anxiety, or stress) the above recommendation was followed; however, in the event that more than 1 item per 7 item scale was missing, then the data for that particular scale at the time-point in question was omitted from statistical analysis. All DASS21 questionnaires/subscales were appropriate for inclusion in the analysis and none of the completed questionnaires had to be excluded because of missing items. The results are shown in Table 9.

Table 9

DASS21 Descriptive Statistics

Timepoint	n	Subscale	M	SD	Range of Response Scores
T1	99	Depression	5.72	5.72	0 – 26
		Anxiety	4.85	4.84	0 – 20
		Stress	7.37	6.73	0 – 28
T2	94	Depression	4.74	5.48	0 – 26
		Anxiety	5.49	5.05	0 – 24
		Stress	5.98	6.62	0 – 32
T3	90	Depression	4.91	6.68	0 – 34
		Anxiety	5.18	4.71	0 – 22
		Stress	5.87	6.74	0 – 32

Note. n = number of subjects; M = mean; SD = standard deviation

Reliability statistics for each time-point for each of the three DASS21 subscales and the total scale for the current study were calculated using Cronbach's alpha and are summarized in Table10. These results are comparable to those reported in the literature with the exception of the reliability coefficient for the anxiety scale in the current study being slightly below the lowest published value of 0.69 (see Chapter 3, page 38 for details and references).

Table 10

DASS21 Reliability Statistics

Timepoint	Cronbach's alpha			
	Depression	Anxiety	Stress	Total
T1	0.78	0.57	0.85	0.89
T2	0.83	0.61	0.87	0.89
T3	0.87	0.58	0.88	0.91

Generalized estimating equations (GEE) statistical analysis was used to look for change over the 3 time-points in the entire study sample. There was a significant improvement in depression at T2 compared to T1 (estimate -1.01, SE 0.48, p <0.035), but not at T3 compared to T1 (estimate -0.88, SE 0.70, p = 0.209). There were no statistically significant changes in anxiety at any of the time-points (T2 vs T1: p = 0.26; T3 vs T1: p = 0.45). Stress did show an improvement at both T2 (estimate -1.59, SE 0.63, p = 0.011) and T3 (estimate -1.66, SE 0.64, p = 0.0097) compared to T1.

The study subjects' symptom severity on the DASS is shown in Figure 3 and will be discussed in detail where applicable in relationship to the research questions.

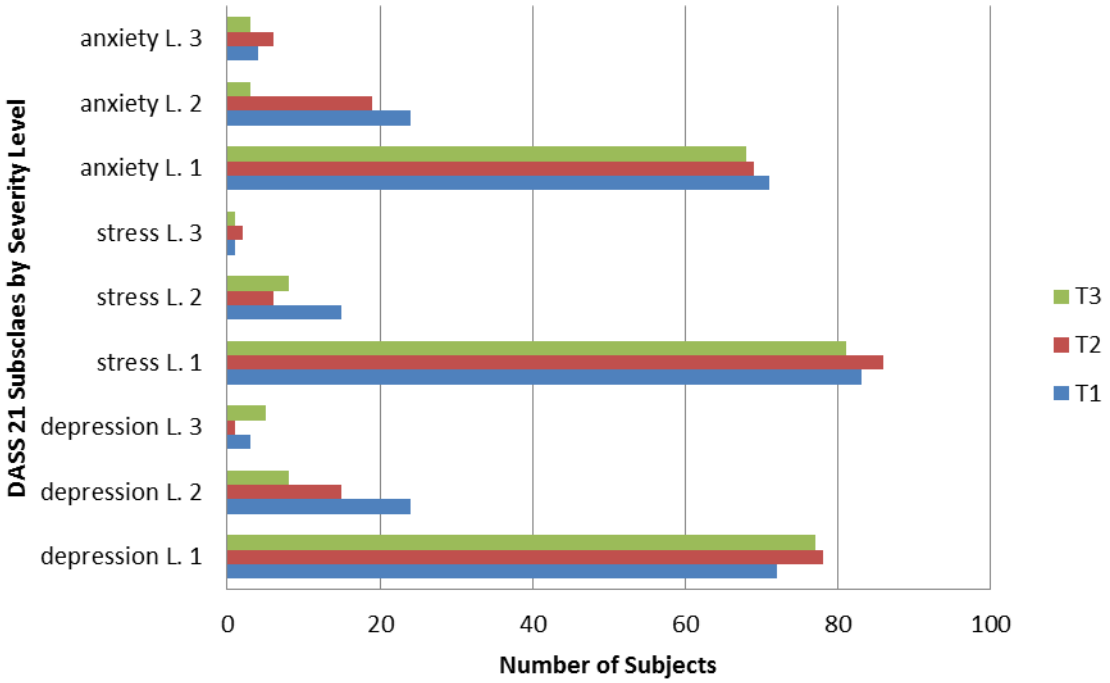

Figure 3. DASS21 subscale symptom severity at T1, T2 and T3 for all study subjects.
At all time-points: Depression L.1, stress L.1, and anxiety L.1 – within normal range;
Depression L.2, stress L.2, and anxiety L.2 – mild – moderate symptoms;
Stress L.3 – severe symptoms;
Anxiety L3 – severe/extremely severe symptoms.
At T1 and T2: Depression L.3 - severe symptoms.
At T3: Depression L.3 – severe/extremely severe symptoms.

FACT/FACIT questionnaires.

All the FACT/FACIT questionnaires have some items which are reverse scored before being added to obtain the subscale totals. A higher score indicates better quality of life or less severe symptoms. The number of study subjects completing the FACIT-Fatigue, FACT-Lym and FACT-Cog subscales at T1 was 100 and at T2 was 94. At T3, FACT-Lym and FACT-Cog were completed by 90 subjects, and the FACIT-Fatigue by 89 subjects.

The FACT/FACIT Scoring Guidelines indicate for all of their questionnaires, subscale scores can be prorated in the event of missing items. A prorated subscale score is calculated as follows:

[Sum of item scores] x [N of items in subscale] ÷ [N of items answered]

Calculating the subscale score as above is considered acceptable as long as > 50% of items were answered. To calculate a total score on a particular questionnaire, the overall item response rate must be > 80% (Functional Assessment of Chronic Illness Therapy (FACIT) website). These conventions have been followed for the calculation of scores in the event of missing data on the FACT/FACIT questionnaires. No FACT/FACIT questionnaires had to be excluded from the analysis because of missing items; however, the QoL items on the FACT-Cog at T1 were not completed by one subject with the result that this particular subscale on that subject's questionnaire was excluded from analysis.

FACT-Fatigue.

The range of scores possible for the FACIT-Fatigue subscale is 0 (very symptomatic) to 52 (no symptoms). The descriptive statistics for the fatigue subscale are provided in Table 11.

Table 11

FACIT-Fatigue Descriptive Statistics

Univariate Statistic	T1	T2	T3
M	36.2	35.63	36.63
SD	11.11	11.38	10.45
Range	11 - 52	7 - 52	10 - 52

Note. M = mean; SD = standard deviation

Overall, on GEE analysis there was no change when considering the entire study sample at either T2 ($p = 0.556$) or T3 ($p = 0.766$) compared to T1. Whilst there was no significant change in fatigue levels for the entire cohort over time, there were individuals who did change either positively or negatively from one assessment time-point to another, and these will be discussed in detail where applicable as they apply to the research question(s).

FACT-Lym.

The FACT-Lym questionnaire consists of 5 subscales: 1) Physical well-being (PWB); 2) Social well-being (SWB); 3) Emotional well-being (EWB); 4) Functional well-being (FWB); 5) Lyms (lymphoma symptoms). The PWB, SWB, and FWB subscales each have a scoring range from 0 – 28. The score range for the EWB subscale is 0 – 24, and for the Lyms 0 - 60. The Total or overall score for the sum of all these subscales

ranges from 0 – 168. The Trial Outcome Index (TOI) is the sum of the PWB, FWB and Lyms subscales. The developer of the FACT/FACIT questionnaires indicates that the TOI is an efficient measure of physical and functional outcomes as the SWB and EWB subscales are more likely to remain relatively stable and not as likely to change rapidly over time in response to chemotherapy (FACIT website).

Table 12

FACT-Lym Descriptive Statistics

Timepoint	N	[a]Subscale	M	SD	Range of Response Scores
T1	100	PWB	22.38	4.56	8 – 28
		SWB	23.35	4.48	6 – 28
		EWB	18.87	3.36	9 – 24
		FWB	17.77	6.34	4 – 28
		Lyms	43.63	8.94	19 – 60
		Total	126.01	21.19	79 – 161
		TOI	83.79	17.53	44 - 114
T2	94	PWB	21.18	5.23	8 – 28
		SWB	24.25	3.82	2 – 28
		EWB	20.01	3.20	10 – 24
		FWB	18.38	6.43	0 – 28
		Lyms	46.81	8.46	21 – 60
		Total	130.64	21.05	65 – 166
		TOI	86.38	17.70	39 - 115
T3	90	PWB	21.74	5.15	8 - 28
		SWB	24.27	3.96	8 – 28
		EWB	19.90	3.73	3.6 – 24
		FWB	19.51	6.32	3.5 – 28
		Lyms	48.02	8.39	17 – 59
		Total	133.45	22.61	49.1 – 167
		TOI	89.27	18.02	29.5 - 115

Note. N = number of subjects; M = mean; SD = standard deviation
[a]PWB = Physical well-being; SWB = social well-being; EWB = emotional well-being; FWB = functional well-being; Lyms = lymphoma symptoms; Total = PWB + SWB + EWB + FWB + Lyms; TOI = PWB + FWB + Lyms

GEE statistical analysis was undertaken on the subject responses to the FACT-Lym at T2 and T3 compared to T1 (see Table 13 for statistical results). This revealed a significant decline in PWB between T1 and T2. There was a slight improvement at T3 compared to T2 but it had not recovered back to the baseline level and was not significant (ns) compared to T1. SWB had improved at both T2 and T3 compared to T1. The estimate, SE and p values at T2 and T3 are virtually identical. EWB had also improved at T2 and at T3 compared to T1, but with no difference between T2 and T3. There was a slight improvement in FWB at T2 compared to T1, but this was ns; however, there was a significant change at T3 compared to T1. With respect to the Lymphoma subscale there was a significant improvement at both T2 and T3 compared to T1. Total score also improved at T2 and T3 compared to T1. There was an improvement at T2 for the TOI, however, this did not reach statistical significance ($p = 0.068$), with further improvement at T3 ($p = 0.001$), both compared to T1.

Table 13

FACT-Lym GEE Results

Subscale	β Estimate (SE)	95% CI	p-value
[a]PWB			
T2	-1.16 (0.53)	(-2.19; -0.12)	0.029*
T3	-0.62 (0.56)	(-1.72; 0.47)	0.264
[a]SWB			
T2	0.95 (0.45)	(0.07; 1.84)	0.034*
T3	0.87 (0.41)	(0.07; 1.67)	0.033
[a]EWB			
T2	1.14 (0.29)	(0.56; 1.71)	<0.001*
T3	1.11 (0.40)	(0.33; 1.89)	0.005*
[a]FWB			
T2	0.53 (0.52)	(-0.48; 1.54)	0.304
T3	1.62 (0.56)	(0.52; 2.73)	0.004*
[a]Lyms			
T2	3.26 (0.73)	(1.83; 4.69)	<0.001*
T3	4.39 (0.80)	(2.82; 5.97)	<0.001*
[a]Total			
T2	4.76 (1.71)	(1.42; 8.10)	0.005*
T3	7.39 (2.06)	(3.34; 11.43)	<0.001*
[a]TOI			
T2	2.65 (1.45)	(-0.20; 5.50)	0.068
T3	5.40 (1.66)	(2.15; 8.65)	0.001*

Note.95% CI = 95% confidence interval.
[a]In reference to T1. *Statistically significant at p <0.05

Research Questions

The remainder of the results of the data analyses will be presented as appropriate in relationship to the research questions.

Research question 1: What are the manifestations of cognitive dysfunction/ impairment over time in non-Hodgkin's lymphoma patients receiving front-line chemotherapy at the Cross Cancer Institute?

FACT-Cog.

FACT-Cog, version 3 (v.3), consists of 37 questions divided over 4 subscales: 1) perceived cognitive impairments (CogPCI) (20 items); 2) impact of perceived cognitive impairments on quality of life (CogQOL) (4 items); 3) comments from others (CogOTH) (4 items); and 4) perceived cognitive abilities (CogPCA) (9 items). Two items pertaining to multitasking in each of the CogPCI and CogPCA subscales are not scored as these were added later and have not yet been validated (J. Bredle, personal communication, October 12, 2014; Joly et al., 2012), thus the range of possible scores for each subscale are: 1) 0 – 72 (CogPCI); 2) 0 – 16 (CogQOL); 3) 0 -16 (CogOTH); 4) 0 – 28 (CogPCA). As with the other FACT/FACIT questionnaires, a higher score indicates fewer symptoms, whereas a lower score is reflective of worse symptomatology. Descriptive statistics for the FACT-Cog for the subjects on this study are reported in Table 14. The questionnaire was completed by 100 subjects at T1, 94 subjects at T2 and 90 subjects at T3. However, at T1, one individual did not complete the quality of life items and thus the results for this subscale are based on 99 subjects.

Table 14

FACT-Cog Descriptive Statistics

Timepoint	[a]Subscale	n	M	SD	Range of Response Scores
T1	CogPCI	100	57.96	11.82	20 – 72
	CogOTH	100	15.02	1.84	5 – 16
	CogPCA	100	21.20	5.65	3 – 28
	CogQOL	99	10.67	4.89	0 - 16
T2	CogPCI	94	56.42	13.98	9 – 72
	CogOTH	94	14.86	2.12	6 – 16
	CogPCA	94	20.26	6.47	0 – 28
	CogQOL	94	12.15	4.24	2 - 16
T3	CogPCI	90	56.88	14.21	0 - 72
	CogOTH	90	14.86	2.12	4 – 16
	CogPCA	90	20.07	6.68	2 – 28
	CogQOL	90	12.09	3.98	0 - 16

Note. n = number of subjects completing each subscale and included in analysis; M = mean; SD = standard deviation.
[a]CogPCI = Perceived cognitive impairment; CogOTH = Comments from others; CogPCA = Perceived cognitive abilities; CogQOL = Impact of perceived cognitive impairments on quality of life

GEE analysis (Table 15) did not show any significant changes at T2 or T3 for perceived cognitive impairment, comments from others or for perceived cognitive abilities, although for the latter at T3, whilst not statistically significant ($p = 0.09$), there was an increase in cognitive concerns when compared to T1. There was a significant reduction in the adverse effect of perceived cognitive impairments on quality of life (CogQOL subscale) at both T2 (β estimate 1.43, 95% CI .037 – 2.49, $p = 0.008$) and T3 (β estimate 1.34, 95% CI .036 – 2.31, $p = 0.007$).

Table 15

FACT-Cog GEE Results

Subscale	β Estimate (SE)	95% CI	p-value
[a]CogPCI			
T2	-1.14 (1.09)	(-3.28; 0.99)	0.29
T3	-0.91 (1.16)	(-3.18; 1.36)	0.43
[a]CogOTH			
T2	-0.14 (0.19)	(-0.51; 0.22)	0.44
T3	-0.17 (0.18)	(-0.52; 0.19)	0.35
[a]CogPCA			
T2	-0.80 (0.57)	(-1.92; 0.32)	0.16
T3	-0.99 (0.59)	(-2.15; 0.16)	0.09
[a]CogQOL			
T2	1.43 (0.54)	(0.37; 2.49)	0.008*
T3	1.34 (0.50)	(0.36; 2.31)	0.007*

Note. 95% CI = 95% confidence interval
[a]In reference to T1. *Statistically significant at $p < 0.05$

The minimum clinically important difference (MCID) was calculated for FACT-Cog for each study subject based on the publication by Cheung et al. (2014) (see chapter 3 for details of how the per item range was calculated). Using the range of 0.19 – 0.29 per item, a MCID range was calculated for each subscale: 1) CogPCI (18 items, MICD range 3.42 to 5.22); 2) CogOTH (4 items, MCID range 0.76 to 1.16); 3) CogQOL (4 items, MCID range 0.76 to 1.16); and 4) CogPCA (7 items, MCID range 1.33 to 2.03). For the purposes of this study, only a decrease in score (i.e., worsening of self-reported cognitive function) between time-points has been considered as a MCID. This is consistent with the report by Cheung et al. who could not establish a MCID estimate for improvement in perceived cognitive function as the associated effect size in their study was too small at < 0.2. The data on the number of individuals who met the criteria for worsening cognitive function based on the MCID is presented in Table 16. The subjects who reported a

decrement in cognitive function were not necessarily the same individuals at each time-point, nor on all subscales (i.e., some individuals had a change across all subscales, whereas others only had a change on one or two of the subscales).

Table 16

Deterioration in Self-Reported Cognitive Function (FACT-Cog) Based on MCID Calculations

		Number of Subjects		
Subscale	[a]Change in score	[b]T1-T2 n/95 (%)	[c]T1-T3 n/89 (%)	[d]T2-T3 n/89 (%)
CogPCI	≥ 3.42	32 (33.7)	29 (32.6)	24 (27)
	≥ 5.00	24 (25.3)	26 (29.2)	19 (21.3)
CogOTH	≥ 0.76	24 (25.3)	24 (27)	16 (18)
	≥ 1.00	24 (25.3)	24 (27)	16 (18)
CogQOL	≥ 0.76	28 (29.5)	24 (27)	37 (41.6)
	≥ 1.00	28 (29.5)	24 (27)	37 (41.6)
CogPCA	≥ 1.33	43 (45.3)	38 (42.7)	28 (31.5)
	≥ 2.00	42 (44.2)	38 (42.7)	28 (31.5)

[a]minimum decrease in score between time-points
[b]number who reported worsening cognitive function at T2 compared to T1
[c]number who reported worsening cognitive function at T3 compared to T1
[d]number who reported worsening cognitive function at T3 compared to T2

Pearson product moment correlation co-efficient statistics were run on the FACT-Cog subscales. The strength of the correlation was determined using the guidelines for *r* published by Muijs (2011): $r = 0 < 0.10$ (weak); $r = 0.10$ to 0.29 (modest); $r = 0.30$ to 0.49 (moderate); $r = 0.50$ to 0.79 (strong) and $r \geq 0.80$ (very strong). There were positive correlations between the four subscales on the FACT-Cog questionnaire, with a strong correlation between CogPCI and each of CogOTH and CogPCA ($r = 0.513$ and 0.553 respectively, $p < 0.001$) at T1. The correlation between CogPCA and CogOTH at T1 was

modest (r = 0.293, p = 0.003). At both T2 and T3, the strength of the correlation between these three subscales was strongly positive: 1) CogPCI and CogOTH (r = 0.674 and 0.760 respectively, p < 0.001); 2) CogPCI and CogPCA (r = 0.673 and 0.764 respectively, p < 0.001); 3) CogPCA and CogOTH (r = 0.529 and 0.596 respectively, p < 0.001). The correlation coefficient analysis for the CogQOL subscale is provided under Research Question 4 later in this chapter.

CogState.

The CogState computerized test battery was competed by a total of 100 subjects at T1, 93 subjects at T2 and 87 subjects at T3. Of these, 6 subjects completed T1 only, 7 subjects completed T1 and T2 only, one subject completed T1 and T3, and 86 completed the testing at all 3 assessment time-points. The tasks on the CogState battery have been analyzed as per the recommendations of the publishers (CogState website). CogState has identified primary outcome measures for each cognitive task which are reported to be the optimal variables for the detection of change at both group and individual levels. These are described in Table 17 and the specific variable(s) to be used for analysis of each task is listed in Table 18. All statistical analyses reported in this paper for the CogState computerized test battery scores are group statistics (i.e., descriptive statistics, change (difference scores) between assessment time-points, and correlation coefficients). The plan is to look at change scores for each subject (calculation of effect sizes/within group analyses) and calculation of composite scores (as per the CogState analysis guidelines) at the end of the study once all subjects have competed all planned assessments (i.e., T1, T2, T3, T4 and T5).

Table 17.

[a]*CogState Tasks*: *Primary Outcome Measures, Unit(s) of Measurement and Description*

Variable	Unit of Measurement	Description
lmn	Log_{10} milliseconds	Speed of performance; mean of the log_{10} transformed reaction times for correct responses. Lower score = better performance
acc	Arcsine square root proportion correct	Accuracy of performance; arcsine transformation of the square root of the proportion of correct responses. Higher score = better performance
err	Total errors	Accuracy of performance; total number of errors across all rounds of the task. Lower score = better performance
ter	Errors	Total number of errors made over all trials while learning the maze pathway, and on remembering the maze pathway after a delay. Lower score = better performance
cor	Number of correct responses	Total number of correct responses made in remembering the list on all trials, and also after a delay. Higher score = better performance
mps	Moves per second	Total number of correct moves per second. Higher score = better performance

[a]Reference: 1) CogState Data Guidelines for Analysis and 2) CogState TPROD006 File Format Specification and Data Description V1, September 2012 (p. 9-13), both available on the CogState website.

The publishers recommend that only data from complete tasks be used for analysis, as scores based on fewer trials (i.e., task only partially completed) are not as reliable as scores based on completion of all trials in the task, and are thus, less likely to reflect the subject's level of performance. In this study, there were four subjects who did not complete one task each out of the complete test battery: 1) GMR at T2; 2) GMR at T1;

3) CPAL at T3; and 4) TWOB at T3. These four tasks for these individuals have thus been excluded from analysis.

Additionally, as per the CogState Data Guidelines for Analysis (CogState website), "… integrity checks can be applied to the data to ensure that each subject is completing each test 'properly' and as expected" (p.8). The minimum accuracy levels CogState has set for the integrity criteria are based on a healthy adult sample and are: Detection – 90% proportion correct; identification – 80% proportion correct; one back – 50% proportion correct; and one card learning – 50% proportion correct. When the integrity checks were run on the CogState study data, the accuracy scores of two individuals on the detection task (both at T2) were significantly below the cut-off level of 90% correct (17% and 0%), thus these two task test results were excluded from analysis. The integrity checks for the other subjects revealed: 1) detection accuracy – a total of 19 subjects were below the > 90% cut-off level, however the majority of these were between 1% - 10% below, with one individual at 13% and one at 20% below the cut-off level; 2) identification accuracy – 11 subjects were below the > 80% cut-off level, with the majority between 2% - 9% below and one at 13% and one at 19% below the cut-off; 3) one card learning accuracy – 11 were below the > 53% cut-off, with all subjects being between 2% - 10% below the cut-off; and 4) one back accuracy – no subjects failed this integrity check. Whilst these subjects' scores were below the respective cut-off for each task, these cut-off levels were based on healthy adults, and as such given that the study population are not "healthy", but have been diagnosed with and required treatment for lymphoma, the decision was made to include their test results in the initial analysis as reported in this dissertation. This decision was made based on studies which have identified the presence of cognitive impairment at

diagnosis, prior to the start of any therapy (Massa et al., 2006; Meyers et al., 1995; Meyers et al., 2005; Wefel, Lenzi, et al., 2004), and it was thought that if these tasks on these individuals were excluded that we may miss impairment if it was present at T1, and the rationale was similar for the subsequent sessions (T2 and T3) (during and after chemotherapy +/- radiotherapy). At the time of the final study analysis (after all subjects have completed all follow-up testing time-points) the plan will be to exclude the tasks that failed the integrity checks and rerun the statistical analyses to determine if any differences in the results are obtained.

Table 18

CogState Descriptive Statistics

[a]Task	[b]Outcome Variable	Time-point	n	Mean (SD)	Minimum	Maximum	SEM
DET	lmn	T1	100	2.56 (.096)	2.4	2.82	0.01
		T2	91	2.57 (.104)	2.38	2.87	0.01
		T3	87	2.57 (.097)	2.38	2.78	0.01
IDN	lmn	T1	100	2.75 (.066)	2.58	2.88	0.01
		T2	93	2.75 (.067)	2.61	2.94	0.01
		T3	87	2.74 (.061)	2.61	2.86	0.01
GMCT	mps	T1	100	1.08 (.306)	0.23	1.83	0.03
		T2	93	1.09 (.288)	0.37	1.67	0.03
		T3	87	1.12 (.278)	0.13	1.63	0.03
GML	ter	T1	100	55.32 (21.9)	17	130	2.2
		T2	93	48.84 (20.6)	19	146	2.1
		T3	87	44.01 (18.6)	17	110	2.0
GMR	ter	T1	98	7.94 (4.28)	1	23	0.43
		T2	92	7.62 (4.22)	0	20	0.40
		T3	86	7.26 (4.04)	0	22	0.44
ISL	cor	T1	100	24 (5.06)	11	33	0.51
		T2	93	25 (5.24)	10	34	0.54
		T3	87	26 (4.84)	11	34	0.52
ISLR	cor	T1	99	8.1 (2.54)	2	12	0.26
		T2	93	8.6 (2.45)	2	12	0.25
		T3	86	8.5 (2.7)	1	12	0.29
OCL	acc	T1	100	0.96 (.103)	0.72	1.15	0.01
		T2	93	0.98 (.101)	0.72	1.19	0.01
		T3	87	1.02 (.096)	0.79	1.21	0.01

(continued)

Table 18 *CogState Descriptive Statistics* (continued)

[a]Task	[b]Outcome Variable	Time-point	n	Mean (SD)	Minimum	Maximum	SEM
ONB	acc	T1	100	1.32 (.159)	0.97	1.57	0.02
		T2	93	1.37 (.140)	0.97	1.57	0.02
		T3	87	1.39 (.147)	0.98	1.57	0.02
ONB	lmn	T1	100	2.93 (.08)	2.76	3.15	0.01
		T2	93	2.91 (.08)	2.75	3.12	0.01
		T3	87	2.89 (.086)	2.64	3.17	0.01
TWOB	acc	T1	100	1.22 (.145)	0.85	1.57	0.01
		T2	93	1.26 (.158)	0.81	1.57	0.02
		T3	86	1.28 (.172)	0.89	1.57	0.02
TWOB	lmn	T1	100	3.01 (.093)	2.81	3.26	0.01
		T2	93	2.99 (.097)	2.80	3.22	0.01
		T3	86	2.97 (.104)	2.71	3.22	0.01
CPAL	err	T1	100	102.69 (58.01)	9	272	5.80
		T2	93	93.69 (59.13)	7	258	6.13
		T3	85	83.92 (59.19)	1	281	6.42
SETS	err	T1	100	34.18 (19.09)	8	80	1.91
		T2	93	30.3 (17.02)	4	66	1.76
		T3	86	28.27 (16.59)	8	72	1.79
SECT	acc	T1	99	1.09 (.136)	0.66	1.37	0.01
		T2	93	1.13 (.127)	0.57	1.32	0.01
		T3	86	1.14 (.131)	0.62	1.38	0.01

Note. n = number of subjects; SD = standard deviation; SEM = standard error of means
[a]DET – detection; IDN – identification; GMCT –Groton maze timed test; GML – Groton maze learning test; GMR – GML delayed recall; ISL – international shopping list; ISLR –ISL delayed recall; OCL – one card learning; ONB – one card back memory; TWOB – two card back memory; CPAL – continuous paired associate learning; SETS – set shifting; SECT – social emotional cognition task.
[b]lmn – speed measure; acc – accuracy measure; err – accuracy measure; mps – moves per second (speed & accuracy measure); cor – correct responses (accuracy); ter – total errors (accuracy)

As can be seen Table 18, there were no differences in the mean scores of the outcome variables for T1, T2 or T3 for the majority of the CogState tasks. The exceptions are for the GML, CPAL and SETS tasks for which the mean (standard deviation) at T1 vs T3 are: 1) GML: 55.3(21.9) vs 44 (18.6); 2) CPAL: 102.69 (58) vs 83.9 (59); and 3) SETS: 34.18(19.1) vs 28.27 (16.6).

Statistical analyses using paired samples t-tests were conducted on each of the CogState tasks using the appropriate primary outcome variable and looking for changes in

scores between time-points T1 and T2, between T1 and T3, and between T2 and T3. There were no statistically significant changes between any of these time-points for the detection (DET), Groton maze timed chase test (GMCT), Groton maze learning test – delayed recall (GMR), or the identification (IDN) tasks. The remainder of the CogState tasks showed statistically significant improvement in change scores between time-points as shown in Table 19. All results, including those that are not statistically significant, are presented.

Table 19

Paired Samples t-Test Statistics for CogState Change Scores

[a]Task	[b]Variable	Time-points	Paired differences				p value
			Mean	SD	95% CI		
					Lower	Upper	
CPAL	err	T1 – T2	6.33	50.12	-3.94	16.60	0.224
	err	T1 – T3	19.38	42.61	10.20	28.56	<0.001*
	err	T2 – T3	10.89	5.01	0.928	20.86	0.033*
DET	lmn	T1 – T2	-0.010	0.086	-0.028	0.007	0.251
	lmn	T1 – T3	-0.013	0.088	-0.032	0.006	0.174
	lmn	T2 – T3	-0.003	0.085	-0.022	0.015	0.739
GMCT	mps	T1 – T2	-0.008	0.226	-0.054	0.039	0.74
	mps	T1 – T3	-0.031	0.216	-0.078	0.015	0.176
	mps	T2 – T3	-0.018	0.181	-0.057	0.021	0.362
GML	ter	T1 – T2	5.44	15.51	2.46	8.41	<0.001*
	ter	T1 – T3	10.37	15.22	7.11	13.64	<0.001*
	ter	T2 – T3	4.92	13.39	2.05	7.80	0.001*
GMR	ter	T1 – T2	0.043	4.41	-0.861	0.946	0.926
	ter	T1 – T3	0.494	4.00	-0.379	1.37	0.264
	ter	T2 – T3	0.446	4.03	-0.433	1.33	0.316
IDN	lmn	T1 – T2	-0.006	0.056	-0.017	0.005	0.306
	lmn	T1 – T3	0.0002	0.055	-0.012	0.012	0.970
	lmn	T2 – T3	0.006	0.046	-0.004	0.016	0.226

*Statistically significant at $p < 0.05$

(continued)

Table 19 *Paired Samples t-Test Statistics for CogState Change Scores* (continued)

[a]Task	[b]Variable	Time-points	Paired differences				p value
			Mean	SD	95% CI		
					Lower	Upper	
ISL	cor	T1 – T2	-1.00	4.25	-1.87	-0.129	0.025*
	cor	T1 – T3	-1.48	4.21	-2.38	-0.575	0.002*
	cor	T2 – T3	-0.465	3.52	-1.22	2.89	0.223
ISLR	cor	T1 – T2	-0.457	1.85	-0.836	-0.079	0.018*
	cor	T1 – T3	-0.212	2.19	-0.683	0.260	0.375
	cor	T2 – T3	0.306	2.21	-0.172	0.784	0.206
OCL	acc	T1 – T2	-0.019	0.107	-0.041	0.003	0.098
	acc	T1 – T3	-0.062	0.089	-0.081	-0.043	<0.001*
	acc	T2 – T3	-0.043	0.079	-0.060	-0.026	<0.001*
ONB	lmn	T1 – T2	0.018	0.07	0.004	0.032	0.012*
	lmn	T1 – T3	0.035	0.07	0.020	0.05	<0.001*
	lmn	T2 – T3	0.014	0.067	-0.0005	0.028	0.057
	acc	T1 – T2	-0.049	0.174	-0.084	-0.013	0.008*
	acc	T1 – T3	-0.062	0.181	-0.101	-0.023	0.002*
	acc	T2 – T3	-0.009	0.184	-0.048	0.031	0.660
SECT	acc	T1 – T2	-0.034	0.114	-0.056	-0.011	0.005*
	acc	T1 – T3	-0.045	0.116	-0.070	-0.020	0.001*
	acc	T2 – T3	-0.008	0.101	-0.030	0.13	0.446
SETS	err	T1 – T2	3.34	15.11	0.246	6.44	0.035*
	err	T1 – T3	4.37	16.57	0.791	7.94	0.017*
	err	T2 – T3	2.05	15.64	-1.33	5.42	0.231
TWOB	lmn	T1 – T2	0.021	0.072	0.007	0.036	0.005*
	lmn	T1 – T3	0.032	0.080	0.015	0.050	<0.001*
	lmn	T2 – T3	0.011	0.073	-0.005	0.027	0.164
	acc	T1 – T2	-0.041	0.151	-0.072	-0.010	0.010*
	acc	T1 – T3	-0.050	0.154	-0.083	-0.017	0.004*
	acc	T2 – T3	-0.003	0.181	-0.042	0.036	0.873

Note: SD = standard deviation; 95% CI = 95% confidence interval; *Statistically significant at $p < 0.05$.
[a]DET – detection; IDN – identification; GMCT –Groton maze timed test; GML – Groton maze learning test; GMR – GML delayed recall; ISL – international shopping list; ISLR –ISL delayed recall; OCL – one card learning; ONB – one card back memory; TWOB – two card back memory; CPAL – continuous paired associate learning; SETS – set shifting; SECT – social emotional cognition task.
[b]lmn – speed measure; acc – accuracy measure; err – accuracy measure; mps – moves per second (speed & accuracy measure); cor – correct responses (accuracy); ter – total errors (accuracy)

Research question 2: What factors predict cognitive dysfunction/impairment experienced by non-Hodgkin's lymphoma patients receiving front-line chemotherapy at the Cross Cancer Institute?

The relationship between perceived cognitive function (measured by FACT-Cog) and perceived fatigue (measured by FACIT-Fatigue) was explored using the Pearson product-moment correlation coefficient at each of the 3 assessment time-points and for each of the four subscales on the FACT-Cog. The strength of the correlation was determined using the guidelines for *r* published by Muijs (2011): $r = 0 < 0.10$ (weak); $r =$ 0.10 to 0.29 (modest); $r = 0.30$ to 0.49 (moderate); $r = 0.50$ to 0.79 (strong) and $r \geq 0.80$ (very strong). There was a strong positive correlation on the CogQOL and fatigue at T1, T2 and T3. A moderate positive correlation was seen for: 1) CogPCI and fatigue at all 3 time-points; 2) CogOTH and fatigue at T2; and 3) CogPCA and fatigue at T1, T2 and T3. CogOTH and fatigue at T1 and T3 both showed modest correlation. Details of the statistical analyses are provided in Table 20.

Table 20

Pearson Correlation Coefficients for FACT-Cog and FACIT-Fatigue

Timepoint	[a]n	FACIT-Fatigue + CogPCI	CogOTH	CogQOL	CogPCA
T1	n	100	100	99	100
r		0.399	0.164	0.525	0.488
p		<0.001*	0.104	<0.001*	<0.001*
T2	n	94	94	94	94
r		0.438	0.343	0.602	0.377
p		<0.001*	0.001*	<0.001*	0.001*
T3	n	90	90	90	90
r		0.478	0.263	0.531	0.419
p		<0.001*	0.012*	<0.001*	<0.001*

[a]n = number of subjects completing FACIT-Fatigue: T1 = 100; T2 = 94; T3 = 90
*Statistically significant at $p < 0.05$

One-way analysis of variance (ANOVA) was conducted to compare scores on the subscales of the FACT-Cog (CogPCI, CogPCA, CogOTH, CogQOL) with the subscales on the DASS21 (depression, anxiety, stress) at T1, T2 and T3. The severity ratings for each of the DASS subscales were collapsed into three categories for the purpose of analysis for this study. The majority of subjects were categorized as within normal limits for depression, anxiety, and stress at each assessment time-point (see *Figure 3* on page 77), and as such, there were too few subjects in the other severity categories to analyze in the 5 severity ratings as published in the DASS manual (Lovibond & Lovibond, 1995). The three symptom severity categories used for this study are: 1) normal; 2) mild/moderate; and 3) severe or severe/extremely severe.

There was a statistically significant difference in the mean value of CogPCI, CogPCA and CogQOL with both the depression and stress subscales of the DASS at T1,

T2 and T3, as well as for CogOTH with the same DASS subscales at T2 and T3. There was a statistically significant difference in the mean value of CogPCI and anxiety at T2 and T3, CogQOL and anxiety at T1, T2 and T3, and with CogPCA and CogOTH and anxiety at T3. Additionally, there was a significant difference in CogOTH with depression and stress at T2 and T3. Figures 4 and 5 are presented as two examples of visual representations of these results. See Table 21 for details of the ANOVA results.

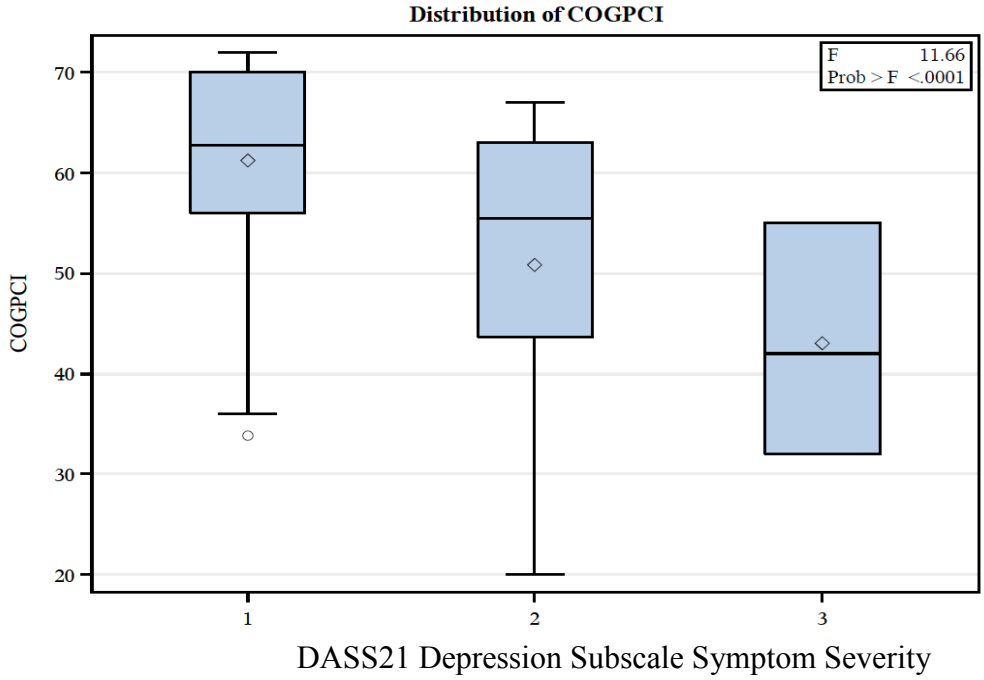

Figure 4. Relationship between perceived cognitive impairment (CogPCI) (measured on the FACT-Cog) and Depression (measured on DASS21) at T1. A higher score on CogPCI indicates fewer symptoms, whereas a higher severity level on the DASS21 indicates more symptoms. ◊ = mean

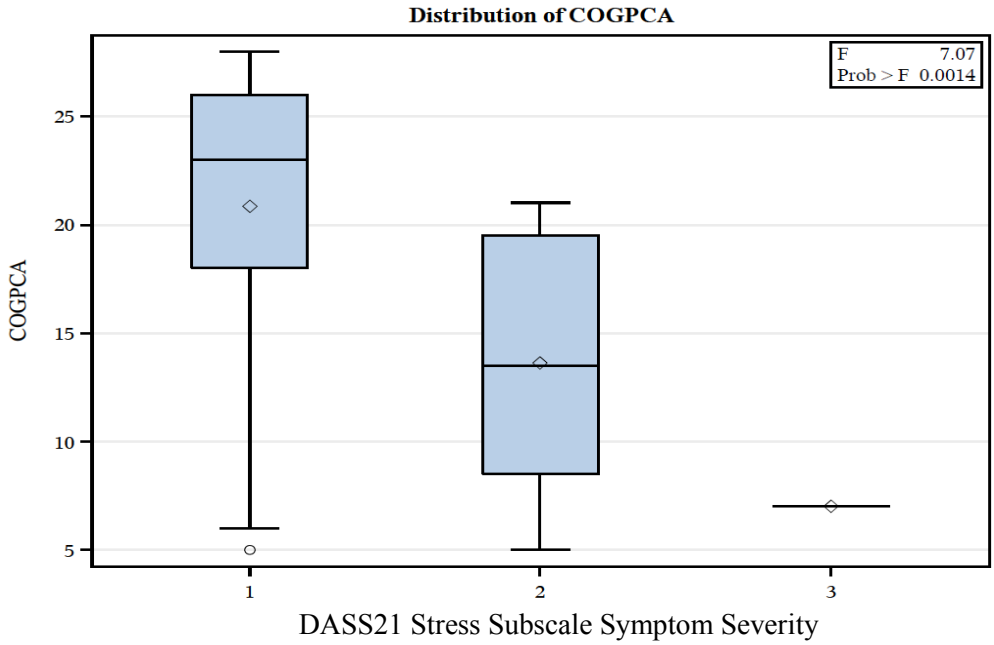

Figure 5. Relationship between perceived cognitive abilities (CogPCA) (measured on the FACT-Cog) and Stress (measured on DASS21) at T3. A higher score on CogPCA indicates fewer symptoms, whereas a higher severity level on the DASS21 indicates more symptoms. ◊ = mean. There was only 1 individual in the DASS severity level 3 at this timepoint.

Table 21

Relationship of FACT-Cog Symptom Scores to DASS21 Symptom Severity at T1, T2 & T3 on One-Way ANOVA

		Depression			Anxiety			Stress		
		[a]MS	F	p	MS	F	p	MS	F	p
Cog PCI	T1	1318	11.7	<0.001*	1105	9.4	<0.001*	1536	14.1	<0.001*
	T2	1783	11.1	<0.001*	260	1.3	0.27	1253	7.3	0.001*
	T3	1765	10.6	<0.001*	2547	17.2	<0.001*	1690	10.1	<0.001*
Cog PCA	T1	220	7.8	<0.001*	132	4.4	0.02*	170	5.8	0.004*
	T2	238	6.4	0.003*	70	1.7	0.19	201	5.3	0.006*
	T3	297	7.7	<0.001*	400	11.0	<0.001*	277	7.1	0.001*
Cog OTH	T1	2.9	0.86	0.43	0.90	0.26	0.77	1.49	0.43	0.65
	T2	28.6	7.2	<0.001*	7.9	1.8	0.17	48	13.8	<0.001*
	T3	16.2	3.9	0.03*	37.6	10.1	<0.001*	19.5	4.7	0.01*
Cog QOL	T1	249	12.9	<0.001*	160	7.5	<0.001*	176	8.4	<0.001*
	T2	199	14.3	<0.001*	57	3.4	0.039*	74	4.5	0.01*
	T3	156	12.4	<0.001*	145	11.4	<0.001*	101	7.3	0.001*

Note. MS = mean square.
*Statistically significant at $p < 0.05$.

Logistic regression analysis was conducted to look for a possible association of the different risk factors with perceived cognitive function. The dependent binary variables were the MCID for each of the subscales on the Fact-Cog. All subjects with change scores that fell within the minimum of the MCID range for the applicable subscale were used for the analysis as per recommendations for analysis of group differences (Yost & Eton, 2005). The independent factors used for the regression analysis included: Sex, baseline ECOG PS (0 + 1 vs 2 + 3), type of chemotherapy (doxorubicin-containing vs non-doxorubicin-containing), age (< 60 yrs vs ≥ 60 yrs), hemoglobin (Hb) level (< 120 gm/L vs ≥ 120 gm/L), fatigue, depression, anxiety, stress, and quality of life (QoL), the latter as measured by FACT-Lym Total score and TOI score. Years of education and menopausal

status were not analysed for correlation with the FACT-Cog MCID. This was due to the fact that in each category one of the subgroups was too small for comparison purposes (< 12 years of education [n = 20] and premenopausal [n = 5] respectively).

For each of the independent variables of hemoglobin (Hb), fatigue, depression, anxiety, stress, and QoL the specific scores entered into the regression analysis were those that were recorded for T2 (for the MCID between T1 and T2) and for T3 (for the MCID between T1 and T3 and between T2 and T3). These values were chosen as the assumption was that if there was a relationship between the independent and dependent variables, the results at the time-point the change score was measured (i.e., T2 or T3) would more likely have an effect on the subjects' self-reported symptoms at that point than the baseline results would have on a change (decline) between T1 and T2 or T3, or the T2 results would have on a change between T2 and T3.

The independent variables found to be statistically significantly related to self-reported (perceived) cognitive function as measured by the MCID change scores were: Male, ECOG PS of 0 or 1, younger age, doxorubicin chemotherapy, higher hemoglobin, fatigue, depression, stress, anxiety, and both the FACT-Lym Total and TOI scores. With the exception of the quality of life measures (FACT-Lym Total and TOI) which are presented in the section pertaining to research question # 4, each of the other factors are discussed in more detail below. Only the statistically significant findings are reported (p value of $\alpha < 0.05$, OR = odds ratio, 95% CI = 95% confidence interval).

Sex.

Males were 75% to 86% less likely than females to report a cognitive decline on the CogPCI, CogOTH, and CogPCA subscales:

Subscale & time-point	OR	95% CI	p value
CogPCI T1-T2	0.222	0.089 - 0.556	0.001
CogPCI T1-T3	0.247	0.096 - 0.636	0.004
CogOTH T1-T3	0.233	0.087 - 0.627	0.004
CogPCA T1-T3	0.135	0.050 - 0.365	<0.001

ECOG PS.

Subjects with a baseline ECOG PS of 0 or 1 were 62% less likely to report a decline on the CogQOL subscale between T2 and T3 compared to those with a baseline PS of 2 or 3 (p = 0.047, OR 0.327, 95% CI 0.109 - 0.986).

Age.

Younger (< 60 years of age) study participants were 70% to 72% less likely to report cognitive decline on the CogPCI and CogOTH subscales compared to those 60 years of age and older:

Subscale & timepoint	OR	95% CI	p value
CogPCI T1-T3	0.300	0.117 - 0.769	0.012
CogOTH T1-T2	0.284	0.105 - 0.772	0.014
CogOTH T1-T3	0.293	0.107 - 0.802	0.014

Doxorubicin chemotherapy.

Doxorubicin chemotherapy was associated with 2.6 times more concerns about cognitive abilities (CogPCA) at T3 compared to T2, compared to non-doxorubicin-containing regimens (p = 0.039, OR 2.603, 95% CI 1.052 – 6.444).

Hemoglobin.

Using the Generalized Linear Model (GLM), when the baseline (T1) Hb level was entered into the regression calculation as the independent variable, a hemoglobin value of 120 gm/L or higher was associated with a 2.26 point higher score on the CogQOL subscale at T1 (p = 0.03, B (SE) 2.26 (1.05), 95% CI 0.200 - 0.432) compared to study subjects with a lower hemoglobin. There were no other statistically significant correlations between baseline hemoglobin and the scores on the other FACT-Cog subscales at T1. On regression analysis a higher hemoglobin at T3 was 60% less likely to be correlated with a decline in CogQOL between T2 and T3 (p = 0.046, OR 0.388, 95% CI 0.153 - 0.982) compared to those with lower hemoglobin levels.

Fatigue.

Subjects reporting less fatigue on the FACIT-Fatigue questionnaire were 4% to 8 % less likely to have a decline in cognitive function on all four subscales of the FACT-Cog compared to individuals with higher levels of fatigue:

Subscale & timepoint	OR	95% CI	p value
CogPCI T1-T3	0.918	0.875 - 0.918	< 0.001
CogPCI T2-T3	0.941	0.898 - 0.985	0.010
CogOTH T1-T2	0.958	0.920 - 0.998	0.038
CogOTH T2-T3	0.950	0.904 - 0.998	0.041
CogOTH T1-T3	0.918	0.918 - 0.965	0.001
CogQOL T1-T2	0.940	0.902 - 0.979	0.003
CogQOL T2-T3	0.959	0.920 - 0.999	0.046
CogPCA T2-T3	0.953	0.913 - 0.994	0.026
CogPCA T1-T3	0.958	0.919 - 0.998	0.042

Depression.

Self-reported cognitive decline was 8% more likely in those with higher levels of depression compared to those reporting fewer depressive symptoms for CogPCI at T3 compared to T2 (p = 0.036, OR 1.077, 95% CI 1.005 – 1.154) and for CogOTH between T1 and T3 (p = 0.032, OR 1.079, 95% CI 1.007 – 1.156). Additionally, whilst not statistically significant (i.e., $p < 0.05$) for cognitive change on CogQOL and CogPCA at T3 compared to T1, the p value for both of these regression analyses was 0.05 and 0.055 respectively. The OR was 1.071 and 1.076 and the 95% CI was 1.000 – 1.146 and 0.999 – 1.160 respectively.

Stress.

The study subjects with higher stress scores were more likely (7% - 11%) to report cognitive decline on the CogPCI, CogQOL, CogOTH and CogPCA subscales:

Subscale & time-point	OR	95% CI	p value
CogPCI T2-T3	1.105	1.029 - 1.187	0.006
CogPCI T1-T3	1.083	1.012 - 1.160	0.022
CogQOL T2-T3	1.069	1.000 - 1.143	0.049
CogQOL T1-T3	1.081	1.009 – 1.158	0.026
CogOTH T1-T2	1.071	1.000 – 1.146	0.049
CogOTH T1-T3	1.090	1.016 – 1.169	0.016
CogPCA T1-T3	1.072	1.002 - 1.146	0.043

Anxiety.

Increased levels of anxiety contributed to a decrease in subjective cognitive function on the FACT-Cog subscales CogPCI, CogQOL and CogOTH. Patients with more anxiety were 9% to 14% more likely to report a decline compared to those with lower anxiety scores.

Subscale & timepoint	OR	95% CI	p value
CogPCI T2-T3	1.138	1.028 - 1.259	0.013
CogPCI T1-T3	1.121	1.016 - 1.237	0.022
CogQOL T1-T3	1.116	1.011 – 1.232	0.029
CogOTH T1-T3	1.138	1.028 - 1.260	0.013

Logistic regression analysis on the change in score between T1 and T2 on the CogQOL subscale and anxiety was not statistically significant, however the p value was 0.052, OR was 1.089 and the 95% CI was 0.999 – 1.187, which equated to those with increased levels of anxiety being 9% more likely to report worsening cognitive function affecting quality of life.

Research question 3: Is there a correlation between objective (neuropsychological) and subjective (perceived) cognitive assessments in non-Hodgkin's lymphoma patients receiving front-line chemotherapy at the Cross Cancer Institute?

A possible correlation between objective cognitive function measured by the CogState test battery and subjective (perceived) cognitive function as measured by the FACT-Cog questionnaire was investigated using the Pearson product-moment correlation coefficient. The analyses were conducted using the scores on each of the three assessment time-points for each subscale on the FACT-Cog (CogPCI, CogOTH, CogPCA, CogQOL) and the CogState tasks, CPAL (paired associate learning), IDN (attention), GML (executive function), GMR (delayed recall), SETS (executive function), and TWOB (complex working memory). These specific tasks were chosen as the cognitive functions they assess are the domains that have been identified as potentially being affected in cancer- and cancer treatment-related cognitive dysfunction. The strength of the correlation

was determined using the guidelines for *r* published by Muijs (2011): $r = 0 - <0.10$ (weak); $r = 0.10$ to 0.29 (modest); $r = 0.30$ to 0.49 (moderate); $r = 0.50$ to 0.79 (strong); and $r \geq 0.80$ (very strong).

The correlation between the FACT-Cog subscales and the remainder of the CogState tasks will be analyzed and published when the follow-up testing is completed. The reason for this is the multiple testing problem that when there are a large number of comparisons (e.g., 10 or more), a new alpha level has to be established to determine statistical significance (Lang & Secic, 2006). One method to obtain the new alpha level is Bonferroni's correction for multiple tests (new alpha = old alpha/n) where n = number of comparisons (e.g., 13 tasks x 3 time-points = 39; p = 0.05 ÷ 39 = 0.0013) (S. Ghosh, personal communication, Nov 26, 2014; Lang & Secic, 2006).

The majority of the results showed no correlation between subjective and objective cognitive impairment with the exception of CPAL at T3, IDN at T1 and T2, GML at T1, SETS at T3, and TWOB at T1 and T2. There was a moderate negative correlation between CPAL and each of the subscales CogPCI and CogOTH at T3 ($r = -0.305$, $p = 0.005$; $r = -0.311$, $p = 0.004$ respectively). There was a modest negative correlation between IDN and: 1) CogPCA at T1 ($r = -0.220$, $p = 0.028$); and 2) each of the subscales CogPCI and Cog PCA at T2 ($r = -0.229$, $p = 0.034$; $r = -0.226$, $p = 0.036$ respectively). GML and CogPCA at T1 showed a modest negative correlation ($r = -0.250$, $p = 0.012$). There was a modest positive correlation between SETS and CogOTH at T3 ($r = 0.247$, $p = 0.023$), between the acc variable on the TWOB and CogPCA at T1 ($r = 2.42$, $p = 0.015$) and between GMCT and CogPCA at T2 ($r = 0.225$, $p = 0.029$). A modest negative correlation

was present between the acc variable on the TWOB and CogPCI at T2 (r = -0.214, p = 0.038). The complete results of the Pearson correlation statistical analyses are reported in Table 22.

Table 22

Pearson Correlation Coefficients for Selected Tasks on CogState and the FACT-Cog Subscales

CogState Task (outcome variable) & Time-point	Statistical measures	CogPCI	CogOTH	CogPCA	CogQOL
CPAL (acc)					
T1	*r*	-0.070	0.489	0.127	0.015
	p	0.567	-0.057	0.210	0.883
T2	*r*	-0.188	-0.178	-0.022	-0.055
	p	0.069	0.086	0.834	0.599
T3	*r*	-0.305*	-0.311*	-0.129	-0.152
	p	0.005*	0.004*	0.245	0.170
IDN (lmn)					
T1	*r*	-0.038	-0.016	-0.220*	0.086
	p	0.706	0.873	0.028*	0.397
T2	*r*	-0.244*	-0.138	-0.203	-0.165
	p	0.018*	0.185	0.050	0.113
T3	*r*	-0.229*	-0.172	-0.226*	-0.187
	p	0.034*	0.113	0.036*	0.085
GMCT (mps)					
T1	*r*	0.151	0.145	0.167	0.141
	p	0.133	0.149	0.098	0.165
T2	*r*	0.175	0.083	0.225*	0.007
	p	0.092	0.427	0.029*	0.943
T3	*r*	0.041	-0.034	0.107	0.054
	p	0.705	0.753	0.327	0.621
GML (ter)					
T1	*r*	0.028	-0.016	-0.250*	-0.003
	p	0.783	0.973	0.012*	0.977
T2	*r*	0.099	-0.005	-0.066	-0.043
	p	0.344	0.961	0.527	0.681
T3	*r*	-0.028	0.021	-0.205	-0.187
	p	0.796	0.849	0.059	0.084

Note. *r* = Pearson correlation coefficient, p = p value. *Statistically significant at $p < 0.05$

(continued)

Table 22 *Pearson Correlation Coefficients for Selected Tasks on CogState and the FACT-Cog Subscales* (continued)

CogState Task (outcome variable) & Time-point	Statistical measures	CogPCI	CogOTH	CogPCA	CogQOL
GMR (ter)					
T1	*r*	-.0126	0.009	-0.154	-0.080
	p	0.213	0.927	0.128	0.435
T2	*r*	0.114	0.180	0.085	0.164
	p	0.286	0.091	0.427	0.125
T3	*r*	0.024	-0.007	-0.038	0.113
	p	0.832	0.949	0.743	0.323
SETS (err)					
T1	*r*	-0.077	0.000	-0.057	-0.120
	p	0.447	0.997	0.576	0.236
T2	*r*	-0.005	0.131	-0.039	-0.128
	p	0.966	0.207	0.706	0.220
T3	*r*	0.176	0.247*	0.104	0.082
	p	0.108	0.023*	0.343	0.455
TWOB (acc)					
T1	*r*	0.109	-0.036	0.242*	0.088
	p	0.280	0.722	0.015*	0.385
T2	*r*	0.214*	-0.112	0.025	0.005
	p	0.038*	0.282	0.813	0.964
T3	*r*	-0.124	-0.178	-0.024	-0.108
	p	0.259	0.104	0.825	0.327
TwoB (lmn)					
T1	*r*	-0.031	-0.015	-0.115	-0.036
	p	0.758	0.882	0.256	0.722
T2	*r*	0.039	0.126	0.100	0.007
	p	0.712	0.224	0.337	0.946
T3	*r*	-0.025	-0.062	0.012	-0.069
	p	0.818	0.574	0.915	0.530

Note. *r* = Pearson correlation coefficient, p = p value. *Statistically significant at $p < 0.05$

Research question 4: Is there a correlation between cognitive dysfunction/ impairment and quality of life in non-Hodgkin's lymphoma patients receiving front-line chemotherapy at the Cross Cancer Institute?

FACT-Lym.

The Total and TOI scores on the FACT-Lym quality of life questionnaire were entered as independent binary variables in the logistic regression analysis as indicated in research question # 3 section above. The Total score comprises the responses to all of the subscales, whereas the TOI score does not include either the social or emotional subscales. Both the Total and TOI scores were significantly associated with declines in the FACT-Cog subscale scores between assessment time-points, with those individuals reporting fewer symptoms being 2% to 6% less likely to report cognitive decline. A lower score on all FACT questionnaires indicates more concerns or symptoms, whereas a higher score is associated with fewer symptoms. Thus, those subjects with a higher score (better self-reported quality of life/fewer symptoms) on the FACT-Lym Total and TOI subscales had fewer self-reported cognitive concerns/impairment (i.e., higher score on the FACT-Cog subscales) as shown below. Conversely, those with lower scores on the FACT-Lym (worse quality of life) had lower scores on the FACT-Cog (more concerns about cognitive function).

FACT-Lym Total subscale.

Subscale & time-point	OR	95% CI	p value
CogPCI T2-T3	0.966	0.944 - 0.989	0.003
CogPCI T1-T3	0.968	0.947 - 0.990	0.004
CogQOL T1-T2	0.963	0.941 - 0.986	0.002
CogQOL T2-T3	0.965	0.943 - 0.987	0.002
CogQOL T1-T3	0.973	0.952 – 0.995	0.014
CogOTH T1-T2	0.975	0.954 - 0.997	0.029
CogOTH T2-T3	0.962	0.938 - 0.986	0.002
CogOTH T1-T3	0.955	0.930 - 0.980	< 0.001
CogPCA T2-T3	0.980	0.960 - 1.000	0 .047

In addition, the regression analysis on the change in scores between T1 and T3 for CogPCA, although not statistically significant, had a p value of 0.052, with a 95% CI of 0.961 – 1.000, and an OR of 0.980, which indicated that those with higher quality of life scores were 2% less likely to report cognitive change. Although small, the correlation is consistent with the regression analysis results for CogPCA at T2 –T3, which was significant with a p value of 0.047.

FACT-Lym TOI subscale.

Subscale & time-point	OR	95% CI	p value
CogPCI T2-T3	0.957	0.930 - 0.985	0.003
CogPCI T1-T3	0.961	0.936 - 0.988	0.004
CogQOL T1-T2	0.951	0.924 - 0.979	0.001
CogQOL T2-T3	0.962	0.937 - 0.987	0.004
CogQOL T1-T3	0.967	0.941 – 0.993	0.013
CogOTH T1-T2	0.972	0.947 - 0.999	0.040
CogOTH T2-T3	0.955	0.926 - 0.985	0.003
CogOTH T1-T3	0.944	0.915 - 0.974	< 0.001
CogPCA T2-T3	0.973	0.949 - 0.998	0.034

FACT-Cog

Pearson correlation coefficient analysis revealed a statistically significant correlation between the FACT-Cog quality of life (CogQOL) subscale and each of the other three subscales at all three assessment time-points. Using the same strength of correlation guidelines as reported previously (refer to Research Questions 1, 2 and 3 in the current chapter) there was a modest correlation with CogOTH and CogPCA at T1 (r = 0.202, p = 0.045 and r = 0.26, p = 0.032 respectively) and a moderate correlation with CogPCI (r = 0.334, p = 0.001). At both T2 and T3 the strength of the correlation was moderate between CogQoL and each of the subscales, CogPCI, CogOTH and CogPCA (r between 0.377 to 0.485, p <0.001).

Results Summary

In summary, a total of 100 subjects (65 males, 35 females) between the ages of 26 to 88 years of age with a diagnosis of lymphoma were enrolled into this study between November 2010 and February 2014. The data analyses for this dissertation includes the first 3 assessment time-points (baseline [T1], midway through the planned treatment [T2] and at completion of the planned therapy [T3]). Statistical analyses on the FACT-Cog data revealed a significant impact of perceived cognitive impairments on quality of life (CogQoL subscale) at T2 and T3; however, there were no changes in the other FACT-Cog subscales between time-points. There was deterioration in perceived (self-reported) cognitive function when the minimum clinically important difference (MCID) was calculated for each study subject with between 24 to 43 subjects reporting at least the minimum decrease in score on the FACT-Cog subscales between assessment time-points.

Analyses of group results on the objective testing measures (CogState) showed either no change or an improvement in scores between time-points on the various tasks (i.e., no decline in cognitive function). Within-subject difference scores/effect size analyses were not run on the CogState tasks at this time, but are planned when follow-up on all study subjects is complete.

Fatigue, depression, anxiety and stress were correlated with perceived cognitive function, with those subjects who reported lower levels of these symptoms also reporting fewer cognitive concerns. The independent factors of male sex, baseline ECOG PS of 0 or 1, age < 60 years, doxorubicin chemotherapy, hemoglobin ≥ 120 gm/L, fatigue, depression, stress, and anxiety were all statistically related to self-reported cognitive function as measured by the MCID change scores. There were modest to moderate statistically significant correlations between subjective (FACT-Cog subscales) and objective (on selected CogState tasks) cognitive impairment using Pearson product-moment correlation coefficient statistics. Those subjects who reported better quality of life/fewer symptoms on the FACT-Lym had fewer self-reported cognitive concerns/impairment on FACT-Cog, whilst those with worse QoL reported more cognitive impairment; however, this effect was relatively small, with those subjects with higher FACT-Lym scores (fewer symptoms) only 2% to 6% less likely to report cognitive impairment compared to the subjects with lower FACT-Lym scores (more symptoms).

Chapter 5: Discussion

The purpose of this study was to investigate the presence of cognitive impairment as a potential chemotherapy related toxicity in lymphoma patients. This report presents the study findings for the first three assessment time-points: Baseline (T1), mid-way through the planned chemotherapy (T2) and approximately one month following completion of the final cycle of chemotherapy (T3). The results are discussed as they pertain to the study's research questions. The related literature is discussed as applicable in each section.

Research Question 1: What are the manifestations of cognitive dysfunction/impairment over time in non-Hodgkin's lymphoma patients receiving front-line chemotherapy at the Cross Cancer Institute?

Subjective (perceived) cognitive function

The FACT-Cog questionnaire measures self-reported (also referred to as perceived or subjective) cognitive function, with higher scores reflecting better function (i.e., fewer concerns regarding cognitive impairment). At a group level, GEE analysis of the four FACT-Cog subscales at each of the three assessment time-points revealed quality of life (Cog-QOL) was impacted less by perceived cognitive impairments midway through the planned treatment and at the completion of therapy compared to the impact at baseline. No other statistically significant cognitive concerns were present at the group level at the three assessment time-points. There were individual subjects who did have a variation in scores between time-points, however given that these were reflective of an improvement for some subjects and a worsening for others, it is likely that on the overall group statistical analysis that these changes (positive and negative) cancelled each other out. Despite this,

the study subjects did have more concerns pertaining to their cognitive abilities (Cog-PCA) after the end of the chemotherapy compared to prior to the start of treatment. Whilst this result was not statistically significant ($p = 0.09$), from the perspective of the study subjects it certainly is possible that they would categorize the reduction in cognitive abilities as clinically meaningful/relevant. Qualitative research studies have been consistent in the characterization of changes in cognitive function from the patient perspective as distressing and having a significant impact on daily functioning and quality of life (Fitch, Armstrong, & Tsang, 2008; Mitchell, 2007; Myers, 2012; Myers, 2013). "The changes may not be entirely evident or noticeable to others, or measured definitively on a standardized scale, but they are very real to the person" (Fitch et al., 2007, p. 185).

A literature search for the FACT-Cog questionnaire turned up only 14 reports with very few studies with a longitudinal design. The majority of the research using this PRO measure is cross-sectional in nature. Cheung et al. (2012) reported the results of a cross-sectional study in Asian breast cancer patients who had either completed chemotherapy within the previous year or who were still receiving chemotherapy compared to patients not on chemotherapy. The FACT-Cog questionnaire was used to assess subjective cognitive functioning. More cognitive concerns were found for the chemotherapy group for perceived impairments (Cog-PCI), cognitive abilities (Cog-PCA), and impact on QoL (Cog-QOL) than the non-chemotherapy group. In a validation study of the French version of the FACT-Cog, Joly et al. (2012) report the group mean scores for each of the subscales, which appear to be similar to the results obtained in my study with the exception of the mean Cog-PCA score in the present study being about 2 points higher than in the French study. However, as there was only one assessment time-point in both

the Cheung and Joly studies, the results are not comparable to the current longitudinal study, in that information on potential change that may or may not have occurred over time is lacking due to the study design. Only one study assessed patients at more than one time-point: Prior to chemotherapy, at Day 1 of cycle 4, and 6 months after the baseline testing (Wagner, 2008). There were no statistically significant differences in the mean change scores on FACT-Cog subscales between assessment time-points (baseline to cycle 4; cycle 4 to 6 months post baseline).

Using the minimum clinically important difference (MCID) calculations for worsening subjective cognitive function as reported for the FACT-Cog subscales (Cheung et al., 2014), a subset of study subjects were found to have had deterioration between time-points. Approximately one third of the study participants reported an increase in cognitive impairment at T2 (33.7%) and at T3 (32.6%), both compared to the baseline (T1) levels. In addition, 27% of subjects reported worsening cognitive impairment at T3 compared to T2. Study subjects reported an increase in concerns regarding cognitive abilities at both T2 (45.3%) and T3 (42.7%) compared to prior to the start of treatment. A decline in perceived cognitive abilities following completion of the chemotherapy, compared to mid-way through the planned treatment was present in 31.5% of subjects. Approximately one quarter of study respondents reported an increase in comments received from others regarding their cognitive function at: 1) T2 (25.3%) and T3 (27%) both compared to T1; and 2) T3 (18%) compared to T2.

The study sample in the Cheung et al. (2014) research were Asian (Chinese) women and as such they caution that the MCID identified in their study may not be

applicable to other ethnic groups given cultural differences in interpreting self-report measures. Despite this, the range of values of per-item change Cheung et al. report for the FACT-Cog is consistent with the MCID/MID ranges reported for other FACT/FACIT questionnaires (Hlubocky et al., 2013; Yost & Eton, 2005) and thus, until further research either confirms or refutes Cheung et al.'s results in other ethnic populations, it is reasonable to use these ranges for calculation of MCID in the current study. Cheung et al.'s publication details the validation of an estimate of MCID for the FACT-Cog; however, it does not provide information on the number of subjects in their study who experienced cognitive decline on each of the four FACT-Cog subscales between assessment time-points. As this group is the first to publish MCID scores for the FACT-Cog, there were no other reports I could locate in the literature to compare the subscale MCID declines found in the current study with results obtained in other research.

A concern that has been raised when interpreting the responses to self-report cognitive function questionnaires has to do with the effect pre-existing knowledge of this potential toxicity has on how patients rate their level of impairment (Schagen, Das, & van Dam, 2009; Schagen, Das, & Vermeulen, 2012). Two separate studies conducted by these researchers in the Netherlands investigated the effect "priming" (i.e., informing patients that chemotherapy has an adverse effect on cognition) and the level of pre-existing knowledge of chemotherapy related cognitive impairment had on breast cancer patients' reports of cognitive complaints. They found that the "priming" intervention was associated with an increase in cognitive complaints compared to those patients who received a "neutral" intervention. However, the groups of patients most impacted were different between the two studies. In the 2009 study by Schagen et al., the patients without

a history of chemotherapy reported more cognitive complaints, whereas in the 2012 study it was those who had received chemotherapy who reported more concerns. The authors speculate this difference may be the result of the level of pre-existing knowledge these patients had regarding chemotherapy and cognition. In the 2009 study, pre-existing knowledge was low, whereas in the 2012 study, knowledge levels were high. Schagen et al. (2012) suggest that in specific individuals previous knowledge regarding the potential relationship between chemotherapy and cognitive impairment may be a prerequisite for priming to exert an effect on the reported symptoms.

In a separate study in Australia, cancer patients attending an outpatient chemotherapy education session were asked what their expectations were regarding the potential for the side effects of nausea, anorexia, fatigue, and feelings of sadness following chemotherapy (Colagiuri et al., 2013). With the exception of fatigue, there was a correlation between the occurrence and severity of these symptoms and pretreatment expectancies. Although cognitive concerns were not included in this study, the results would seem to be consistent with those reported by Schagen et al. (2009, 2012). The concept of conforming to what is expected is referred to as “stereotype threat” (Schagen et al., 2009, 2012), and whilst not discounting the very real side effects, including cognitive changes, patients experience as a consequence of chemotherapy, these studies lend credence to the role and contribution psychological factors may have in the incidence and severity of symptoms reported by patients. Thus, a potential limitation of self-reporting is that patients may over-estimate the degree of impairment they actually are experiencing.

For the purposes of this dissertation, I have not calculated either the total scores or the MCID for the individual cognitive domains on the FACT-Cog (e.g., memory, concentration, etc.); therefore, at this point the specific cognitive domains the study participants may have perceived as being more problematic have not yet been identified. This will be interesting to investigate at the conclusion of the study once all of the follow-up testing is complete. As well, within-subject change between time-points for perceived cognitive function has not been calculated for this report, but is planned at the completion of the study.

Objective cognitive function

Objective cognitive function was assessed using the computerized neurocognitive test battery, CogState. For the purposes of this dissertation, statistical analyses were conducted at the group level: Within-subject analyses will be done at the completion of the follow-up assessments. On review of group mean and standard deviation for the detection (DET), identification (IND), one card learning (OCL), and one card back (ONB) tasks, these results are comparable to those published by Fredrickson et al. (2010) for healthy volunteers aged 50 years or older. The overall OCL mean accuracy score in the current study was marginally lower at 0.98 compared to 1.03 in the healthy volunteers in the Fredrickson et al. study.

Paired samples t-test statistics to look at the direction of change scores between testing time-points showed no deterioration in performance on any of the tasks. However, a statistically significant improvement was seen on nine of the thirteen tasks over time: Visual learning and episodic memory (CPAL); spatial working memory and error

monitoring (executive function) (GML); verbal learning (ISL) and verbal learning delayed recall (ISLR); visual recognition memory and attention (OCL); working memory and attention (ONB and TWOB); executive function (SETS); and social emotional cognition (SECT).

In a study using the CogState tasks to assess cognitive function in a group of community dwelling older healthy adults, Darby et al. (2012) report a slight improvement in performance by the group as a whole over the 12 months of testing, despite the fact that there were individuals who experienced a decline in cognitive performance on the task(s). A number of authors have reported that the CogState battery of tasks has shown stability over time, on within-subject change and effect sizes, even when the tasks were repeated at short intervals between testing (Fredrickson et al. 2010; Hammers et al. 2011), including in a recently published study in healthy adult volunteers (Darby et al., 2012); their conclusions are that the effects of practice on performance on the CogState battery of tasks are negligible. As a result, based on the group analyses which has been conducted at this time in the current study, a conclusion cannot be drawn as to the potential reason for an improvement in performance (i.e., learning effects, the presence of baseline cognitive impairment which then subsequently improved, or subtle changes in the scores of those who had a decline in cognitive function which was cancelled out by those who did not decline).

The improvement in performance over time for the group in the current study is not consistent with the findings from most of the reported studies, in which cognitive impairment was documented (e.g., Ahles et al., 2003, Bender et al., 2001; Dietrich et al.,

2008; Salminen, 2005). However, it must be noted that the majority of research has been cross-sectional and as such, the results of neuropsychological testing in these studies provide a snapshot of the individual's cognitive function at one specific point-in-time (Janelsins et al., 2014), rather than an indication of any changes that may have occurred over time. Despite these findings, a few studies in cancer patients have reported improvement on neuropsychological testing on repeat assessments. Jacobsen et al. (2004) reported an improvement in cognitive performance between the baseline (pretreatment) assessment and prior to the start of cycle 4 chemotherapy for the entire group, but when they analyzed subgroups based on change in hemoglobin levels a significant decline was found. A meta-analysis of studies in breast cancer patients found that when patients' results were compared to their own baseline, there was an improvement in performance on neuropsychological testing (Falleti et al., 2005). Falleti et al. (2005) note the improvement in cognitive function is inconsistent with most of the cross-sectional studies which show a decline, and they speculate that the psychological burden, stress and depression associated with a diagnosis of breast cancer is reduced by initiation of curative treatment. Other possible explanations they propose are the effects of practice and learning on test outcomes, or normal variability in performance over time.

More recently, longitudinal studies have been completed and reported, some of which have shown conflicting results with respect to objective testing. Collins, MacKenzie, Tasca, Scherling, and Smith (2013) found significant declines in working memory and processing speed, and verbal and visual memory in breast cancer patients over time as they progressed through their planned course of chemotherapy. All aspects of verbal memory were found to be impaired in 13% of colon cancer patients following

completion of adjuvant chemotherapy (Cruzado et al., 2014). A meta-analysis of 17 studies in breast cancer patients revealed small effect sizes for deterioration in verbal ability and visuospatial ability, but with no impairment in any other cognitive domains (Jim et al., 2012). On the other hand, a few studies have reported no worsening of cognitive function in ovarian and testicular cancer patients receiving chemotherapy (Hensley et al, 2006; Pedersen et al., 2009).

Darby et al. (2012) make a distinction between the identification of cognitive decline and cognitive impairment. For cognitive decline, each person is used as their own control, whereas "comparison of the individual's performance with normative data that is appropriate in terms of demographics, mood, and medical history" (Darby et al., 2012, p. 95) is required for documenting cognitive impairment. Even when the level of performance remains within normal limits, measurement of change allows for the detection of a true deterioration in cognitive function (Darby et al., 2012). The authors discuss a method to detect cognitive decline through the calculation of slopes of performance versus time for each individual, generating normative ranges for these slopes and then applying these to the study data to identify those individuals who have had an abnormal decline over the time frame of the study. Using this method, they were able to identify participants in their study of healthy older adults who had a significant decline and who required additional testing to rule out early AD. This may be an approach to consider at the completion of the current study, in addition to the within-subject change/effect size statistical analysis recommended by the publishers of the CogState battery. Despite the fact that there was no deterioration in performance on group analyses in the current study, when the results of the outcome variables over time were reviewed

for individual study subjects, it was noted that there were some participants who did have what would appear to be quite significant changes (decline) in performance; therefore, it will be interesting to see what the statistical analysis of the within-subject/individual change will reveal.

Research Question 2: What factors predict cognitive dysfunction/impairment experienced by non-Hodgkin's lymphoma patients receiving front-line chemotherapy at the Cross Cancer Institute?

There were no significant differences in self-reported levels of fatigue mid-way through the planned therapy or after the end of the therapy compared to prior to the start of chemotherapy on group analysis. However, on review of individual subject responses, there were some patients who reported either worsening or improvement and it is likely that these differences cancelled each other out on the statistical analysis. Within-subject analysis and minimally important differences (MID) (either improvement or worsening) in fatigue levels over time with treatment are two alternate statistical approaches which may be conducted to assess for changes that occur in this group of patients ("FACIT-F Scale Report," 2013; Yost & Eton, 2005). This analysis has not been conducted at this time, but will be looked at after all follow-up testing is completed.

Fatigue has been identified as a contributing factor to cognitive impairment (Cimprich, 1995; Cimprich & Ronis, 2003; Meyers, 2000; Valentine & Meyers, 2001; Winningham et al., 1994). Despite the fact that no overall change was identified in fatigue for the group, there was a correlation between fatigue and perceived cognitive function. Those subjects with less fatigue reported less cognitive impairment as well as fewer

problems with perceived cognitive abilities at all time-points. The strength of the correlation for both of these was moderate (r = 0.30 to 0.49). There was also a modest (r = 0.10 to 0.29) to moderate correlation between less fatigue and subjects reporting receiving fewer comments from others regarding the noticeability of cognitive impairment at T2 and T3. There was a modest (r = 0.163) but not statistically significant (p = 0.104) correlation at baseline. In qualitative studies of patients with advanced cancer, Olson and colleagues documented a correlation between the level of fatigue (conceptualized as distinct states of tiredness, fatigue, and/or exhaustion) and the severity of perceived cognitive problems (Olson, 2007; Olson, Krawchuk, & Quddusi, 2007; Olson et al., 2008). As patients moved among the three states, their subjective cognitive difficulties also varied in severity, ranging from forgetfulness when tired, to difficulty concentrating with fatigue, and when exhausted they reported what they described as confusion (for example, difficulty navigating a familiar route).

One-way ANOVA revealed a statistically significant relationship between the symptoms of depression, anxiety, and stress and each of the subscales on the FACT-Cog questionnaire. Specifically, those reporting higher levels of depression, anxiety, or stress reported more cognitive concerns, and those with lower levels of these symptoms had fewer cognitive concerns. Perceived cognitive impairments (CogPCI subscale) and perceived cognitive abilities (CogPCA subscale) were both statistically significantly related to depression and stress at all 3 time-points, and to anxiety at T1 and T3, but not at T2. The impact of cognitive concerns on quality of life (CogQoL) was statistically significantly related to each of the symptoms of depression, anxiety, and stress at all 3 time-points. The levels of depression and stress at T1 and T3, and anxiety at T3 were

significantly related to the comments subjects received from others regarding their cognitive function. More self-reported cognitive concerns were related to higher levels of depression, anxiety, or stress and lower levels of these symptoms resulted in fewer cognitive concerns being reported by study subjects. Logistic regression revealed that those with more symptoms were between 7 – 14% more likely to report worse cognitive function than those subjects with lower levels of depression, anxiety, or stress.

Psychological/emotional distress in the form of the symptoms of anxiety, depression, and stress is known to adversely impact cognitive function (Asher, 2011; Kurita et al., 2009). These symptoms have been documented in the literature to be associated with an increase in perceived cognitive problems in cancer patients (Cull et al., 1996; Schagen et al., 2008; Shilling & Jenkins, 2007; van Dam et al., 1998). Consistent with the results of the current study, a correlation between FACT-Cog scores and anxiety and depression has been reported by other researchers (Cheung, 2012; Jacobs et al., 2007; Von Ah & Tallman, 2014; Wagner, 2008). Stress was not assessed as a separate symptom in these studies; however, Reid-Arndt and Cox (2012) conducted a study in breast cancer patients following surgery, but prior to any other therapy with the specific aim of investigating stress and coping styles on cognitive function. They found a relationship between stress and performance on cognitive testing, with the subjects who reported higher levels of stress performing worse on tests of memory, verbal fluency, and attention.

Other factors found to be associated with perceived cognitive function were male sex, ECOG PS of 0 or 1, younger age, doxorubicin chemotherapy and a higher hemoglobin level. Males were approximately 75% less likely to report cognitive decline

than were females. Most of the research to date has been in women with breast cancer, with only a few studies in other tumour types including males. Research into those cancers that affect both men and women would potentially help in sorting out if there are differences between the genders that contribute to different incidences of cognitive complaints and a decline in performance on objective test measures.

Subjects with a better baseline performance status (ECOG of 0 or 1) were significantly less likely to report an adverse impact of cognitive impairment on quality of life at T3 (end of chemotherapy) compared to those with a worse PS at baseline (ECOG of 2 or 3). However, baseline PS did not have an effect on any of the other FACT-Cog subscales at any time-points. It is not exactly clear how a worse baseline PS would impact QoL at T3 and yet not have any impact on any of the other FACT-Cog subscales; however, it is possible that those with more symptoms at baseline (as measured by PS) took longer to recover than those with fewer (or no) baseline disease related symptoms and thus attributed reduced QoL to cognitive changes. I did not collect data on ECOG PS at each of the assessment time-points, which in retrospect would have been easy to do. However, my sense is that an impact on perceived cognitive function would not be apparent from a statistical standpoint, as the majority of patients responded well to the treatment without experiencing significant physical side effects, and would have been classified as ECOG of 0 or 1, and as such there would be too few patients with a worse PS to be able to perform a subgroup analysis.

Younger age (less than 60 years) was significantly associated with fewer cognitive complaints over time, when compared to those subjects 60 years of age and older. The

younger age group was 70% less likely to report cognitive impairment after the end of chemotherapy, compared to baseline, and also less likely to report receiving comments from others regarding their cognitive function both mid-way through and at the end of the treatment compared to baseline. This is perhaps not surprising as age is a known risk factor for cognitive decline (Ahles, Root, & Ryan, 2012; Joshi & Morley, 2006; Lange et al., 2014; Mandelblatt, Jacobsen, & Ahles, 2014). Ahles et al. (2010) found that age greater than 60 years and pre-treatment cognitive reserve were related to a decline in post treatment processing speed in patients exposed to chemotherapy. In their review, Mandelblatt et al. (2014), report that in studies of older patients with breast and prostate cancer the cognitive domains impacted included verbal memory, visual memory, visual-spatial domains, executive function, and/or processing speed. Ahles et al. (2012) suggest that the incidence of cognitive deficits found in any particular study may be impacted by factors such as age and cognitive reserve, with the result that fewer changes may be evident in a study sample composed of young, highly educated individuals compared to one that includes older, less educated patients.

It has been suggested that the type of chemotherapy may impact the development of cognitive impairment with the anthracycline, doxorubicin, considered as having a potential causal role, possibly related to cytokine induced inflammation and oxidative stress (Aluise et al., 2010; Joshi et al., 2005; Joshi et al., 2007; Tangpong et al., 2007). Recent work by Liu, Zhang, Coughlin, Cleary, and Byrne (2014) in cultures of rat cortical neurons and sensory neurons of *Aplysia* (a marine mollusk) found that doxorubicin had an effect on the kinases involved in memory, ERK and MAPK, suggesting that doxorubicin may impair the formation of long term memory. Therefore, for the purpose of the logistic

regression analysis, the chemotherapy regimens were divided into 2 groups: Doxorubicin-containing vs non-doxorubicin-containing regimens. Those individuals who received doxorubicin as part of their chemotherapy regimen were 2.6 times more likely to express concerns about their cognitive abilities at T3 (after completion of planned chemotherapy) than those subjects who did not receive doxorubicin. Decrements in memory, attention, visuospatial skills, and executive functions were found on neuropsychological testing in breast cancer patients (Jansen, Cooper, Dodd, Miaskowski, 2011), and on the domains of verbal memory and psychomotor functioning in breast and lymphoma patients (Ahles et al., 2002) following the receipt of chemotherapy that included doxorubicin. [18F] FDG-PET imaging in lymphoma patients treated with doxorubicin containing regimens (CHOP+/-R; ABVD) showed a lower rate of glucose metabolism predominately in the prefrontal cortex, involving both the cortex and white matter after chemotherapy, compared to those patients who were scanned prior to the start of treatment (Baudino et al., 2012). It will be interesting to see if those subjects who received doxorubicin have a higher incidence and/or greater change on the objective (CogState) testing over time when the within-subject analysis is obtained at the completion of the study.

Low hemoglobin levels are thought to potentially contribute to cognitive impairment in cancer patients (Cunningham, 2003; Jansen, Miaskowski, Dodd, Dowling, & Kramer. 2005b; Mancuso et al., 2006). Hemoglobin level (or anemia) has not been analyzed as a potential risk factor for cognitive dysfunction in the majority of studies (Vearncombe et al., 2009). Anemia with hemoglobin levels less than 120 gm/L was associated with worse performance on tests of attention and visual memory in cancer patients receiving chemotherapy for a variety of tumour types (Jacobson et al., 2004). A

sub-clinical decline in hemoglobin levels between assessment time-points predicted for, and was found to be associated with, impairment on multiple cognitive tests in breast cancer patients on chemotherapy (Vearncombe et al., 2009).

For analysis purposes for this study, hemoglobin was divided into two groups: Less than 120 gm/L (lower Hb group) and 120 gm/L or higher (higher Hb group). A higher baseline Hb was associated with a 2.26 higher score on the effect of perceived cognitive impairment on quality of life subscale (i.e., higher scores represent better quality of life with perceived cognitive impairment having less of an impact on QoL compared to lower scores) at T1 compared to those with hemoglobin levels less than 120 gm/L. A higher Hb level at T3 was less likely to be associated with a worse impact of cognitive impairment on quality of life compared to those with a lower hemoglobin level. In clinical practice we see patients adapting to their symptoms and in particular to a chronically lower hemoglobin level without experiencing the same impact on quality of life as when the change in level is more acute. This has been referred to as response shift (Ahmed & Ring, 2008; Cella, Hahn, & Dineen, 2002; Hamidou, Dabakuyo, & Bonnetain, 2011), in which an individual's reference point changes over time as a result of "adaptation or change in perspective or values based on experience" (Cella, Hahn et al., 2002, p. 388). This process may be beneficial to the patients, resulting in adaptation to the effects of the disease and or its' treatment (Hamidou et al., 2011). Consequently, patients may attribute more meaning to small improvements than to declines of the same magnitude (Cella, Bullinger, Scott, Barofsky et al., 2002; Cella, Hahn et al., 2002).

Strong statistical correlations between any factors and cognitive impairment may be difficult to obtain due to the multifactorial nature of cognitive impairment (Cheung et al., 2013; Kurita et al., 2009; O'Farrell, MacKenzie, & Collins, 2013). It is possible that the contribution of each of the various risk factors is small, but when combined together in the 'right' mix there is an additive or synergistic effect resulting in the perception that deterioration in cognitive function is more pronounced and more likely to be noticed by the affected individual.

Research question 3: Is there a correlation between objective (neuropsychological) and subjective (perceived) cognitive assessments in non-Hodgkin's lymphoma patients receiving front-line chemotherapy at the Cross Cancer Institute?

No correlation was found between the group scores on the majority of the CogState tasks (objective neurocognitive assessment) and the FACT-Cog subscales (subjective or perceived cognitive assessment). Although only modest in strength, a worse performance on the visual attention task (IDN) correlated with a higher level of perceived cognitive impairment at T2 and T3, and with more concerns regarding perceived cognitive abilities at T1 and T3. On the working memory and attention task (TWOB), a modest correlation was found, with a worse performance on the task associated with more perceived cognitive impairments at T2 and with more concerns about cognitive ability at T1. This was also the case for the spatial working memory and error monitoring (executive function) GML task and perceived cognitive abilities at T1. The reverse was true for all of these correlations (i.e. fewer cognitive concerns were associated with a better performance on the CogState tasks). Only one recently published study in 88 breast

cancer survivors who were on average 5 years post treatment, found significant correlations between the FACT-Cog subscales and neuropsychological test results (Von Ah & Tallman, 2014). After controlling for potentially confounding factors (age, depression, anxiety, and sleep), perceived cognitive impairments were significantly correlated with delayed verbal memory, and perceived cognitive abilities were correlated with both immediate and delayed verbal memory and executive function. Jacobs et al. (2007) found a correlation on the "other people noticed deficits" subscale with executive function in a group of patients who were 6 to 12 months post hematopoietic stem cell transplant, but there were no correlations between any of the other FACT-Cog subscales and objective testing measures. Vardy et al, (2006) and Wagner (2008) both reported no significant correlations between the FACT-Cog and neuropsychological test results, however in the former study, Vardy notes that the sample size was small (n=31) and as such the study may have been under-powered to find a correlation even if one existed.

On two of the CogState tasks in the current study a worse performance was associated with fewer cognitive concerns and conversely, a better performance on the tasks was associated with more cognitive concerns. These tasks were: 1) the visual learning and episodic memory task (CPAL) and both the perceived cognitive impairments and comments from others subscales of the FACT-Cog at T3; and 2) the executive function task (SETS) and comments received from others at T3. Similar finding have also been reported by other researchers in breast cancer patients: 1) Falleti et al., (2007) reported more accurate scores on a learning task were associated with lower scores (i.e., more cognitive concerns) on a subjective cognitive performance questionnaire; 2) in a separate study, a moderate association between better self-reported cognitive function and

impairments in selected attention, visuospatial working memory and visual delayed recall NP measures was found (Mehnert et al., 2007); and 3) in the study by Ganz et al., (2013), women with more executive function complaints performed better on visual memory NP tests. It is difficult to know how to interpret these findings, as this is not what would intuitively be expected. Despite what seems to be a contradictory finding, it is possible that patients perceive that they are having more difficulty with their cognitive functioning, yet are still able to successfully complete the tasks on the test battery. One possible explanation is suggested by the results of a MRI study of twins, one of whom was treated for breast cancer, which showed an expanded area of brain activation during a working memory processing task in the twin with breast cancer compared to the healthy twin (Ferguson, McDonald, Saykin, & Ahles, 2007; McDonald, Saykin, & Ahles, 2008). This occurred in the absence of objective cognitive impairment on neuropsychological assessment, but in the presence of greater self-reported cognitive concerns, raising the possibility of compensatory recruitment of additional brain regions in order to successfully perform a given task (Ferguson et al., 2007; McDonald et al., 2008). The authors speculate that this may result in patients perceiving tasks as being more difficult or require more effort to successfully complete than they required previously, and that this may possibly provide an explanation for the discrepancy seen between self-reported cognitive symptoms and the lack of objective findings on neuropsychological assessment.

Additionally, in the current study, the strength of the correlation on group analysis is only modest at most, (r = -0.305 to -0.311 for the CPAL task; r = 0.247 for the SETS task) and as such it is possible that these findings do not actually represent a true relationship. It has been postulated patients may ascribe normal memory and cognitive

lapses to cancer and the associated treatment rather than to either pre-existing problems or to the effects of other disease and treatment related symptoms such as depression, anxiety, fatigue, etc. (Hutchinson, Hosking, Kichenadasse, Mattiske, & Wilson, 2012; Vardy et al., 2006). However, the questions on the PRO measures do not ask patients to make a distinction between cognitive changes and concerns related to cancer therapy or other possible causes: The items on the questionnaires simply ask patients to indicate if they have been experiencing cognitive problems and how frequently these occur. There were patients in my study who advised me when we met for the cognitive testing that the difficulties they reported on the FACT-Cog were unrelated to chemotherapy, but were the result of alternative causes such as not sleeping well or were pre-existing (e.g., "always had to make lists").

In general, no or only weak correlation of subjective cognitive function and objective testing has been reported in the literature (Hutchinson et al., 2012; van Dam et al., 1998; Vardy et al., 2006). In contrast, a statistically significant association between higher levels of memory and/or executive function complaints and poorer performance on visual and verbal memory tests were found in approximately 20% of women with breast cancer on endocrine therapy (Ganz et al., 2013). One reason for the lack of correlation between self-reported and neuropsychological test results that has been proposed is that the controlled testing environment does not replicate or reflect real-world cognitive requirements (i.e., lack of ecological validity) (Cull et al., 1996; Rugo & Ahles, 2003; Schagen et al., 1999; Tannock et al., 2004; van Dam et al., 1998).

Research question 4: Is there a correlation between cognitive dysfunction/impairment and quality of life in non-Hodgkin's lymphoma patients receiving front-line chemotherapy at the Cross Cancer Institute?

Quality of life was measured by the FACT-Lym questionnaire at each assessment time-point. Additionally, there are four questions on the FACT-Cog directed at the effect cognitive impairments have on QoL (CogQOL subscale). The correlation between cognitive impairment and self-reported quality of life on the FACT-Lym is discussed below.

The level of physical well-being declined between the baseline assessment prior to the start of chemotherapy and at the second assessment (mid-way through the planned therapy) and then improved after the end of the chemotherapy, although at that point it had not yet recovered back to the baseline level. This most likely reflects the fact that the majority of subjects had no or minimal symptoms at the start of treatment (ECOG PS of 0 or 1), and then experienced side effects from the chemotherapy which adversely affected their sense of physical well-being. This would be consistent with what is seen in clinical practice where some patients experience a greater impact on quality of life from side effects than other patients do.

Social and emotional well-being both improved at the second assessment and was maintained at the end of treatment compared to the pre-treatment time-point. The reason for this may be that once patients commenced on treatment for their lymphoma, both they and their families/friends were able to cope better with the diagnosis, communicating and

supporting each other in a more effective manner. This is consistent with what is observed in clinical practice.

Functional well-being improved after the completion of the chemotherapy +/- radiotherapy, but not mid-way through the treatment. This may be as a result of side effects experienced during the treatment, which contribute to a reduction in tolerance of physical activities. Once the treatment is discontinued, the adverse effects improve/resolve allowing the patients to resume their usual activities including employment.

The responses to the lymphoma symptoms subscale on the FACT-Lym questionnaire revealed significant improvement (i.e., fewer symptoms) by the second assessment time-point. This is what would be expected, as lymphoma generally responds rapidly to chemotherapy, and as such, disease related symptoms resolve fairly quickly for the majority of patients.

The study subjects' quality of life had improved by the second assessment, with an even greater improvement after the end of the treatment as measured on the global (TOTAL) score on the FACT-Lym. When the emotional and social well-being subscales of the FACT-Lym are excluded from the total score (TOI score), improvement was not statistically significant ($p = 0.068$) at T2, but was significantly improved at T3 ($p = 0.001$). This likely is a reflection of resolution of side effects once the treatment (chemotherapy +/- radiotherapy) is completed. A positive correlation was found between the TOTAL and TOI scores and the Fact-Cog subscales over time. Poorer quality of life was associated with more perceived cognitive complaints on all subscales (i.e., impairments, capabilities, comments from others, and impact of impairments on QoL). This is consistent with other

studies which have also found a correlation between cognitive complaints and quality of life measures (Cheung et al., 2012; Lai et al., 2009; Mehnert et al., 2007).

The impact of cognitive impairments on quality of life as measured by the CogQOL subscale of the FACT-Cog was more pronounced as patients progressed through their planned treatment. Using the MCID change scores between time-points, when compared to baseline 29.5% and 27% of subjects reported a deterioration in QoL mid-way through the planned treatment and after completion of therapy respectively, whilst 41.6% reported a deterioration in QoL after completion of chemotherapy compared to half-way through the treatment. Additionally, there was a strong (r = 0.50 to 0.79) correlation between fatigue and QoL (as measured by the CogQOL subscale on the FACT-Cog) with those subjects who reported less fatigue also reporting less of an impact of perceived cognitive impairment on QoL at all three time-points.

There is often an increase in toxicities with cumulative dosing of the chemotherapy, with the result that patients frequently will report lower energy levels, more fatigue, and an increase in general sense of unwellness/malaise as they receive more cycles of chemotherapy. Consequently, it is possible that the reported effect of cognitive impairment on QoL actually reflects these cumulative changes, but which the patients attribute to cognitive impairments. For example, on review of individual subject responses to the FACT-Cog items, I noticed that some of the study participants indicated they had no cognitive concerns, but reported an effect on QoL on the CogQOL subscale. Without a qualitative component to the study, where patients are interviewed regarding their

rationale for responding in a certain way, it is impossible to know what factors may have contributed to their ratings on the CogQOL questions.

Limitations of the Study

The majority of the study subjects were of Caucasian ethnicity, English speaking and with a grade 12 or higher education; therefore, the results may not be generalizable to the general population with lymphoma. Additionally, the participants were interested in the concept of "chemo-brain", motivated to participate in the study, and a number mentioned that they were interested "in helping others" by participating in the research. It is possible that this group may have a higher level of cognitive functioning, be better able to manage the emotional stresses related to a diagnosis of cancer and its' treatment and as well did not have significant co-morbidities which potentially might have had an impact on cognitive function. For all of these reasons, the study participants are highly selected and thus, may not be the same as those who declined to take part.

The computerized neurocognitive test battery, CogState, uses playing cards for a number of the tasks. Individuals who regularly play cards (such as bridge) and are practiced in remembering specific cards played may perform better on certain tasks (Fredrickson et al., 2010). As well, subjects who regularly play video or computer games may also possibly perform better on some of the tasks (Pietrzak et al., 2008).

Patients with lymphoma who were not on treatment were not included as a control group in the study; thus, it is impossible to know if there may be a difference between the study subjects and patients not on chemotherapy. There were only a few subjects who received a shorter course of chemo (i.e., 3 cycles), therefore no comparisons were possible

between these subjects and those who received the longer course of treatment (≥ 6 cycles). Cumulative toxicity associated with a longer duration of chemotherapy may result in patients experiencing more cognitive impairment compared to fewer cycles of treatment (Ahles et al., 2002; Wienke & Dienst, 1995). Collins et al. (2013) found a consistent worsening of cognitive function in a group of breast cancer patients over time as they progressed through their chemotherapy course from baseline (prior to the start of treatment) through the end of the sixth cycle of chemotherapy, reaching statistical significance following the fourth cycle of treatment. However, in order to successfully complete well-powered prospective studies comprised of multiple groups (e.g., no treatment, short duration of chemotherapy, longer duration of therapy) to confirm the results of prior research, this will require large multi-centre studies (Janelsins, Kesler, Ahles, & Morrow, 2014; Wefel et al., 2011).

There was an improvement in performance on the CogState tasks over time. This leads to the question as to whether this is related to learning effects, rather than an improvement in cognitive function. The statistical analysis on the CogState data was run on group data; the published incidence of cognitive decline on neuropsychological testing ranges from 15 – 25% (Ahles, et al., 2012) and as such, within-subject analysis will be required to identify the small subset of patients who fall within this category. As well, cognitive decline in patients on chemotherapy is generally subtle in nature, with cognitive functioning remaining within normal limits (Ahles et al., 2002; Ahles et al., 2003; Schagen et al., 1999; van Dam et al., 1998). Therefore, it is possible that evidence of cognitive impairment will not be apparent on group statistics, and that within-subject

analysis will be required in order to reveal those individuals who may have had deterioration in performance on specific tasks in the current study.

Summary

This study is one of the first to investigate the relationship of cognitive impairment to chemotherapy in patients with lymphoma. The results presented in this report include the first three assessment time-points (baseline, mid-way through treatment, and end of treatment). For the purposes of this interim report, the data were analyzed using group statistics, with the plan to run the within-subject change scores/effect sizes at the end of the study when all patients have completed follow-up assessments.

An increase in self-reported cognitive concerns over time was present in a substantial subset of participants on all FACT-Cog subscales: 33% experienced worsening cognitive impairments; up to 45% reported increased concerns regarding cognitive abilities; up to 25% reported receiving more comments from others regarding their cognitive function; and up to 41% reported cognitive impairment was affecting their QoL.

With respect to the objective cognitive testing, improvement was seen between time-points, in the domains of visual learning and episodic memory, executive function, verbal learning, visual memory, working memory, attention, and social emotional cognition. Whilst this is not what might have been expected, given that these results are based on group analysis of all study participants, declines in individual scores may not be evident until the within-subject analyses are completed.

Correlations between several risk factors and subjective cognition over time were identified. These included fatigue, depression, anxiety, and stress, with higher levels of each being associated with the reporting of increased cognitive concerns. Male sex, ECOG PS of 0 or 1 at baseline, and age less than 60 years were all correlated with fewer cognitive complaints. Receiving doxorubicin as part of the chemotherapy regimen was related to an increase in self-reported cognitive concerns. A modest to moderate correlation was found between the cognitive domains of visual attention, working memory, attention, and executive function (spatial working memory and error monitoring) and both perceived cognitive impairments and cognitive abilities, with a worse performance on the tasks measuring these domains being associated with more cognitive complaints. However, on two of the tasks measuring visual learning, episodic memory, and executive function, a modest correlation was present, but with a better performance being associated with more study subject reported cognitive concerns. Similar findings have been reported in the literature. Quality of life correlated with perceived cognitive functioning with worse QoL on the FACT-Lym being associated with increased cognitive complaints as recorded on the FACT-Cog.

With respect to the FACT-Cog subscale measuring the impact of cognitive impairments on QoL, up to 41% of subjects reported deterioration in QoL related to cognitive impairment over time. A strong correlation between fatigue and impact of cognitive impairment on QoL was also seen at all time-points.

The results of this interim analysis reveal that some lymphoma patients on chemotherapy do experience perceived cognitive changes as they progress through

treatment and that these changes can have an adverse impact on quality of life. The implications for practice, education, and research of these findings as well as of cancer- and treatment-related cognitive deficits in general are discussed in Chapter 6.

Chapter 6: Implications

This longitudinal study investigated cognitive function in lymphoma patients receiving front-line chemotherapy. The results presented in this dissertation include the data up to the third assessment time-point (end of planned treatment), with the statistical analyses based on the group data; within-subject analysis will be conducted when the ongoing follow-up testing is completed. The implications of the study results and of cognitive impairments associated with cancer and cancer treatment for practice, education, and research are discussed in this chapter. However, it is possible that additional implications for one or more of these areas may become apparent when the more detailed final data analysis is completed.

Practice

A question that arises as a consequence of research into cancer- and cancer treatment-associated cognitive change is: "What is the best method for assessing cognitive function in the practice setting?" Neuropsychological assessment and neuroimaging are not feasible in clinical practice owing to a number of issues including cost and resources (e.g., staff with expertise in the assessment modality, availability of equipment, length of time required for testing, funding to pay for the testing, etc.) (Wagner et al., 2009). This makes a self-report measure of cognitive function attractive from a practical point of view (Asher, 2011; Lai et al., 2009; Wagner et al., 2009), as it can be completed by the patient in a minimal amount of time, thus reducing patient burden, and with minimal assistance from clinic staff. Communication between clinicians and their patients regarding cognitive concerns can be facilitated by the use of a valid perceived cognitive function PRO

measure (Lai et al., 2009). The FACT-Cog is one such PRO measure and was developed for assessment of the nature, severity, and impact of cognitive deficits (Jacobs et al., 2007; Lai et al., 2009; Wagner et al., 2009). Although the statistical analyses in the current study for this report have been performed on group data, decrements in cognitive function, as reported on the FACT-Cog, including an impact on QoL were found. Additionally, although there are a limited number of research studies published using the FACT-Cog at this time, those that have been reported have also documented a decline in perceived cognitive function, at least in a subset of patients (Cheung et al., 2012; Cheung et al., 2014; Joly et al., 2012; Von Ah & Tallman, 2014). The FACT-Cog assesses perceived cognitive impairments, abilities, comments from others (i.e., noticeability of cognitive changes to others), and impact of these concerns on quality of life: This makes it a more comprehensive self-assessment tool than some of the other PRO measures for determination of subjective cognitive functioning which only have 1 or 2 questions asking about difficulties with concentration and remembering (e.g., EORTC QLQ-C30 [EORTC website], MD Anderson Symptom Inventory [Jones et al., 2013]). It is routine practice in clinical settings for patients to complete short questionnaires intended to provide an assessment of other symptoms they may be experiencing, such as pain, nausea, fatigue, etc. Nursing staff are the health care providers (HCPs) most frequently responsible for at least the initial review of the responses with the patients, obtaining further details regarding the specifics of the problem(s) including the efficacy of interventions that may have been tried, providing counseling, education, and appropriate referrals to assist the patient with optimizing management of the symptoms. Therefore, it would be appropriate for nurses to review the PRO measures and assess for cognitive complaints at the same

time they are addressing the impact and management of any other symptoms the patient is experiencing.

One issue with the FACT-Cog is that it contains both positively and negatively worded items, and as such when reviewing the responses it will be necessary to ensure that the patients have actually read the questions and confirm with them, if necessary, that they have responded appropriately. This is not only a concern with the FACT-Cog as inaccurate responses have been recorded with other questionnaires used routinely in the clinic as a consequence of patients not reading the instructions correctly (e.g., on a scale of 1-10 (best to worst), marking "10" for all questions, when in fact they had no symptoms and had interpreted "10" as reflecting the best that they could feel). Given that patients often report difficulties with attention, concentration, and information processing speed (Bender et al., 2001; Lange et al., 2014) it may be tempting to attribute these errors in completion of the questionnaires as being related to cognitive impairment; however, whilst this may be a potential contributor for some patients, I do not believe that this would be accurate in a number of cases. This is because when the responses were reviewed and confirmed with the patients, the majority (if not all of them) stated that "I did not read the question" or "I was in a hurry", subsequently correcting their answers.

Another issue with questionnaires such as the FACT-Cog, if used in clinical practice, is where the paper copies would be kept, especially with the trend to eliminate paper charts in favour of electronic medical records (EMR). Whilst the patient's responses at any one time-point are important and have implications for counselling, education, referrals to relevant specialists, etc. at the time of that particular clinic visit, it would be

valuable to have the previously completed forms available for reference in order to determine if the patient is reporting a change, either a decrement or improvement in specific areas, as this may impact the suggestions provided to them by the HCP and for follow-up and evaluation of the effectiveness of any potential interventions previously suggested. One option would be to have the responses entered electronically into the EMR; however, this then becomes a resource issue of who would be responsible for this task. Alternatively, the form could be in an electronic version which the patient could complete on a tablet or laptop, and then the responses saved in the EMR; however, this could be impractical especially in a busy outpatient clinic if it was expected that every patient coming to the OPD would complete the form at every visit (e.g., funding (or lack thereof) for purchase and maintenance of the equipment, number of tablets/laptops required, who is responsible for transferring the completed forms to the EMR, privacy concerns, etc.).

Given that not every patient experiences cognitive dysfunction, it may not be necessary to have every patient complete a cognitive function PRO measure at every clinic visit, but perhaps could be restricted to those who were reporting concerns to the HCP (RN, APN, MD) regarding their cognition at the time they are assessed in clinic. A more comprehensive assessment could then be conducted in those most likely to be affected and thus more likely to benefit from potential interventions. Ongoing and future research may find that only a few domain-specific directed questions are all that are required to accurately reveal cognitive impairment, which could then easily be added to existing symptom directed questionnaires.

Even without chemotherapy older individuals are at increased risk for cognitive impairment, owing in part to lifestyle and other factors such as smoking, obesity, limited physical activity, diabetes, cardiovascular disease, and/or a genetic predisposition (Lange et al., 2014; Mandelblatt, Jacobsen, & Ahles, 2014). Half of all cancers occur in patients age 70 and older: These patients average three co-morbidities in addition to cancer, with cognitive dysfunction frequently among them (Extermann, 2005). There have been few studies enrolling elderly patients with cancer, although some research studies have included older individuals with breast and prostate cancer (Lange et al., 2014; Mandelblatt et al., 2014). The mean age at time of enrollment into the current research study was 61 years; older age was found to be a risk factor for self-reported cognitive impairment with those less than 60 years of age being approximately 70% less likely to report cognitive decline that those 60 years of age and older. Implications of this finding for clinical practice are that HCPs be cognizant of the potential problems and effects on daily activities that cognitive impairment may have on the elderly. This could include difficulties with such tasks as meal planning and preparation, bill payment, following medical advice, managing multiple medications, and performing work related duties (Hodgson et al., 2013; Mandelblatt et al., 2014; Mayo et al., 2014), in addition to any other activities requiring concentration, attention, multitasking, executive functioning, and speed of information processing (Hodgson et al., 2013). Surveillance and screening for cognitive impairments in the elderly is an important component of care for this group of cancer patients (Mandelblatt et al., 2014), and if present, initiation of appropriate counselling, education, and referral, including for geriatric assessment if necessary, should be promptly instituted to prevent worsening of the symptoms to the point where the

patient may no longer be able to perform his/her daily activities. In some cases, dose modification or even a treatment rest may be the most appropriate approach, especially if it is uncertain if the medication is contributing to the symptoms and if the patient is experiencing significant issues with daily functioning. Of course, this must be balanced with the potential risk of inadequate disease control as well as respecting the patient's wishes. One of the greatest fears of older adults is a reduction in cognitive abilities; thus, the potential for systemic therapy to cause adverse cognitive effects may impact treatment decision making and clinical management of these patients, especially in cases where indications for therapy are equivocal (Mandelblatt et al., 2014).

Another potential implication of cognitive impairment for practice pertains to the ability of the patients to remember and follow instructions for activities including those for self-care or taking oral medications (either for symptom management or the novel oral chemotherapy agents). In addition to confirming that patients are taking the prescribed oral medications, nurses and pharmacists can provide suggestions on methods to facilitate compliance (for example, use of a daily/weekly pill dispenser, use of a calendar diary to record when the medications are taken, requesting the pharmacist/pharmacy to package the oral medications in blister packs, referral to home care, etc.). If patients are giving themselves subcutaneous injections such as low molecular weight heparin or hematopoietic growth factors, the nurse should assess on an ongoing basis, not only at the time of initial teaching but also later, that the patient continues to correctly self-administer these medications. In the event that it is determined that the patient is having difficulty self-administering such medications, then it is incumbent on the nurse to explore

alternative options for safe administration of the medication such as a family member, referral to home care, or the patient's community pharmacist.

The correlation between other symptoms, including psychological and emotional factors, and cognitive impairment would suggest that adequately addressing these symptoms may be effective at reducing the severity and in some cases perhaps eliminating the cognitive deficits that some patients experience. A systematic review and meta-analysis found that exercise was effective at reducing fatigue and improving quality of life in breast cancer patients and survivors (McNeely et al., 2006). Although cognitive function was not addressed in this review, given the correlation between symptoms such as fatigue and cognitive complaints, it is conceivable that by reducing fatigue and other adverse effects, that cognitive impairments may be reduced. In an analysis of data collected in the Canadian Community Health Survey (2005-2006 and 2009 – 2010), Neil, Gotay, & Campbell (2014) found that individuals with cancer were more likely to be inactive compared to both those who had never been diagnosed with cancer or those who were cancer survivors. Even though there is limited evidence available at this time to recommend a specific exercise prescription that will reduce the adverse effects of cancer treatment (Campbell, Neil, & Winters-Stone, 2012), given the known benefits of exercise (including on cognition) (Hillman, Erickson, & Kramer, 2008; Voss et al., 2011), a potential implication for oncology HCPs is to assess the level of physical activity their patients are participating in and to encourage regular physical activity (Campbell et al., 2012), using the currently published guidelines for physical activity in cancer survivors (Rock et al., 2012; Schmitz et al., 2010).

Education

"Oncology nurses are key to identifying patients at high risk for chemotherapy-related side effects, assessing patients for potential sequelae, and providing accurate and appropriate patient and family education about expected and potential toxicities" (Myers & Teel, 2008, p.726). In a descriptive pilot study utilizing a survey for data collection (Myers & Teel, 2008), it was found that the majority (94%) of oncology nurses were familiar with the concept of cognitive impairment as a potential toxicity of chemotherapy and believed that it would have a negative effect on the patients' quality of life. Despite this, only 38% of respondents reported assessing their patients for cognitive problems, less than half indicated that they provided education to patients and families on the topic, and almost 75% reported they lacked access to relevant educational material and tools (Myers & Teel, 2008). For nurses and other health care professionals to be adequately prepared to provide comprehensive education and support to their patients with the objective of reducing the potential morbidity of the treatment, it is necessary that they have an understanding of: 1) normal cognitive functioning; 2) the cognitive domains and associated areas of the brain potentially impacted by cancer and/or chemotherapy; 3) the multifactorial effects of various risk factors on cognitive function; 4) the potential impact of cognitive deficits on the patient; 5) the effect of aging on cognition; and 6) the research being conducted.

The fact that a significant proportion (25% - 45% of subjects in the current study) of cancer patients report changes to their cognitive function has implications for the education of nurses and other health care professionals. Similar to the education that

currently occurs with respect to hematological and non-hematological toxicities of chemo- and radio-therapy, the potential for the development of adverse cognitive effects related to cancer and cancer therapy needs to be incorporated into education programs for nurses and other HCPs. Regardless of the potential etiology of cognitive impairment in the oncology population (i.e., the disease itself, chemotherapy effects, other medications, anxiety, depression, fatigue, etc.), the symptoms are very real and distressing to the patients (Fitch, Armstrong, & Tsang, 2008; Mitchell, 2007; Myers, 2012; Myers, 2013), and thus, this is a topic that should be incorporated into educational programs, whether those are at the undergraduate level, orientation classes for new nurses starting a career in oncology, or as part of continuing education initiatives for those professionals working with cancer patients. Enhanced knowledge levels regarding the various aspects related to cancer- and cancer treatment-associated cognitive impairments will result in improved clinical assessment, patient and family education, and with a better understanding of the interaction between various risk factors and cognitive impairment, HCPs will be able to suggest potential interventions, with the ultimate aim of providing comprehensive patient care which addresses all areas of patient concerns.

Research

The analyses completed for this report were at a group level, therefore the foremost implication for research at the completion of the follow-up assessment on all remaining study subjects, will be to look at within-subject change scores/effect sizes over time to obtain a more detailed picture of any cognitive decrements occurring in a subset of participants in this study. Additionally, it will be important to run correlation statistics

between the various risk factors and the objective test results in those individuals who have experienced a change in cognitive function as measured on the CogState tasks, for the purpose of determining which (if any) factors may be contributing to cognitive impairment in this group of patients with lymphoma.

Another area that could be explored is the MCID for the FACT-Cog PRO measure. The work by Cheung et al. (2014) was the first to report MCID scores for this questionnaire, and as such given that this study has five assessment time-points this would be an opportunity to confirm their results in a different ethnic population and in a study which included both men and women (Cheung et al.'s study sample were Asian women with breast cancer).

The majority of the research to date investigating cognitive function in cancer patients has been in women with breast cancer (Hodgson et al., 2013) and with relatively few of those studies including older individuals (Lange et al., 2014). The current study is one of only a few studies in patients with lymphoma (excluding primary CNS lymphoma) and to my knowledge, based on a literature search competed as recently as January 2, 2015, is the first prospective longitudinal trial completed in patients with lymphoma receiving standard dose chemotherapy. As such, additional research is required in patients with hematological malignancies as well as in patients with other tumour types to obtain a more complete picture of the frequency of cognitive dysfunction and the cognitive domains involved in patients with diagnoses other than breast cancer.

In a study by Zimmer et al. (2014) lymphoma patients who received bendamustine and rituximab (BR) were found to have more cognitive impairment on neuropsychological

testing at the end of chemotherapy than those who received R-CHOP, however there were no differences in subjective complaints between the two treatment groups. These results are different than the findings in my research study in which those who received doxorubicin-containing chemotherapy (R-CHOP) reported more subjective concerns. The study by Zimmer and colleagues was cross-sectional with the testing completed once between 4 to 12 weeks after completion of treatment, with a small sample size of 30 subjects with 14 of those receiving R-CHOP and 16 receiving BR; thus it is not directly comparable to the current trial. Correlation statistics between the type of chemotherapy and the neuropsychological (CogState) test results have not yet been completed in the current study, but will be at completion of the follow-up assessments. It will be interesting to see if the results for the objective testing and within-subject analysis of subjective cognitive concerns confirm that doxorubicin-containing chemotherapy confers a higher risk for cognitive impairment than non-doxorubicin-containing regimens.

Although a variety of interventions have been investigated in small studies, none can yet be recommended due to insufficient data and methodological limitations (Fardell et al., 2011). A variety of approaches have been tried (Fardell et al. 2011), including among others: Pharmacotherapy with a number of different agents (Davis et al, 2013; Kohli et al., 2009); a cognitive-behavioural program (Ferguson, Ahles et al., 2007); EEG biofeedback (Alvarez et al., 2013); and yoga (Galantino et al., 2012). Exercise and physical activity have been shown to have a positive effect on cognitive functioning across the lifespan (Hillman, Erickson, & Kramer, 2008; Voss et al., 2011). The chemotherapy drugs, 5-fluorouracil and oxaliplatin, either alone or in combination, are associated with both short and long term cognitive impairment in rodents (object

recognition, spatial reference memory, and contextual fear recall). However, when combined with exercise (4 weeks of wheel running) these effects were ameliorated with the exercising rats performing nearly equivalent to the control animals (Fardell et al., 2012).

The role of exercise and its ability to attenuate the cognitive problems reported by cancer patients is currently being studied. One such investigation is an ongoing proof of concept RCT in post-menopausal breast cancer patients who are younger than 65 years of age and who are experiencing perceived cognitive changes (Campbell, 2014). Participants undergo neuropsychological and exercise testing, fMRI and EEG, then complete the exercise intervention with a goal of 150 minutes of aerobic exercise per week, with repeat testing at the end of the intervention period (Campbell, 2014). I did not collect data on the level of physical activity the study participants were engaging in, although this is information that could have been obtained either as part of a paper questionnaire or via interview prior to completing the CogState battery of tests. Information on physical activity has not been collected or reported in published studies investigating cognitive function in cancer patients, except for those designed to specifically test exercise as a potential intervention.

The multifactorial nature of cognitive impairment lends itself to additional analysis of the quality of life data, as well as the data on depression, anxiety, stress, and fatigue. Sleep dysfunction has been associated with reduced cognitive functioning (Spira et al., 2008): Using the FACT-Cog to assess perceived cognitive function, correlations between subjective cognitive impairment and sleep problems have been documented in breast

cancer survivors (Von Ah & Tallman, 2014) and in patients with head and neck cancer (Rogers et al., 2008). Sleep disturbance is therefore another potential aspect that could be considered for inclusion into the design of future research studies. Another avenue for research is to determine if adequately addressing and instituting appropriate interventions to ameliorate or reduce the severity of other symptoms, reduces the incidence and severity of cognitive complaints.

Inclusion of the collection of blood samples for various biomarkers would also add additional information on the potential underlying pathophysiology of cognitive changes related to cancer and cancer treatment. Markers of inflammation (e.g., IL6, IL-1β, TNF-α.), oxidative stress, and genetics (APOE, COMT), etc. have been implicated as exerting an adverse effect on cognition (Ahles & Saykin, 2007; Nelson et al., 2007; Janselsins et al., 2014). The original plan was to collect blood samples for banking so that testing for some of these biomarkers could have been undertaken, however, unfortunately, this was not possible due to lack of funding for this research project. It is hoped that in the future, this will not be a limiting factor and that biomarkers will be able to be included as part of future study designs.

Conclusion

This study was designed to investigate cognitive changes occurring over time in lymphoma patients receiving standard dose chemotherapy. Patients attending a tertiary cancer centre in Alberta were recruited, with a total sample size of 100 subjects enrolled. The results reported in this dissertation include the first three assessment time-points (baseline, mid-way through the planned treatment, and at the end of therapy) with a data cut-off date of September 24, 2014.

A subset of subjects reported worsening of perceived cognitive function over time as they progressed through their course of chemotherapy, with up to 41% of subjects reporting deterioration in quality of life as a consequence of cognitive impairment. A worse quality of life was associated with more subjective cognitive complaints. Analysis of the objective (neuropsychological) testing using the group data showed a statistically significant improvement on 9 of the 13 CogState tasks over time, which although not what might have been expected, is consistent with the results reported by other researchers (Falleti et al., 2005; Jacobsen et al., 2004). However, when the outcome variables for individual study subjects were reviewed, some participants appear to have had quite significant worsening of performance with repeat testing. It is anticipated that the within-subject analysis, which is planned at the completion of all follow-up visits, will provide additional information on the presence of cognitive impairments in a subset of study participants.

Correlations were seen between the symptoms of fatigue, depression, anxiety, and stress and perceived cognitive impairment, with those subjects who reported more severe

symptoms also reporting greater concerns regarding their cognition. Study participants who were less likely to report cognitive impairment included: 1) Males; 2) those with a better performance status at baseline; and 3) those who were less than 60 years of age. Doxorubicin-containing chemotherapy was associated with an increase in concerns about cognitive abilities, compared to non-doxorubicin-containing regimens. A higher baseline hemoglobin (120 gm/L or higher) was associated with less impact of perceived cognitive problems on QoL prior to the planned chemotherapy compared to a lower hemoglobin level, whereas there was no relationship between hemoglobin level and perceived cognitive function as measured by the other three FACT-Cog subscales (perceived impairments, perceived abilities, and comments from others) at that time-point.

Modest to moderate correlations were seen between the objective tasks measuring visual attention, working memory, attention, and executive function and perceived (subjective) cognitive concerns. As mentioned previously, the data analyses for this report were performed on group statistics, with the intention to run within-subject change scores/effect sizes for both the subjective and objective test results when all study subjects have completed the follow-up assessments. This will provide a more complete picture of the incidence of cognitive impairment over time and the cognitive domains impacted in this group of lymphoma patients.

To my knowledge, this is the first longitudinal, prospective study investigating cognitive function in lymphoma patients receiving standard dose chemotherapy. As such, the results of the study will add important information to the literature in this group of patients. Potential implications for practice, education and research have been suggested.

Given the potential impact cognitive impairment can have on patients' quality of life and daily functioning, additional research in patients with lymphoma, as well as other hematological malignancies is required. Ultimately, the hope is that as the body of knowledge regarding cancer- and cancer treatment-related cognitive dysfunction increases, this will translate into enhanced quality of care and more effective management of this potentially devastating symptom for affected individuals.

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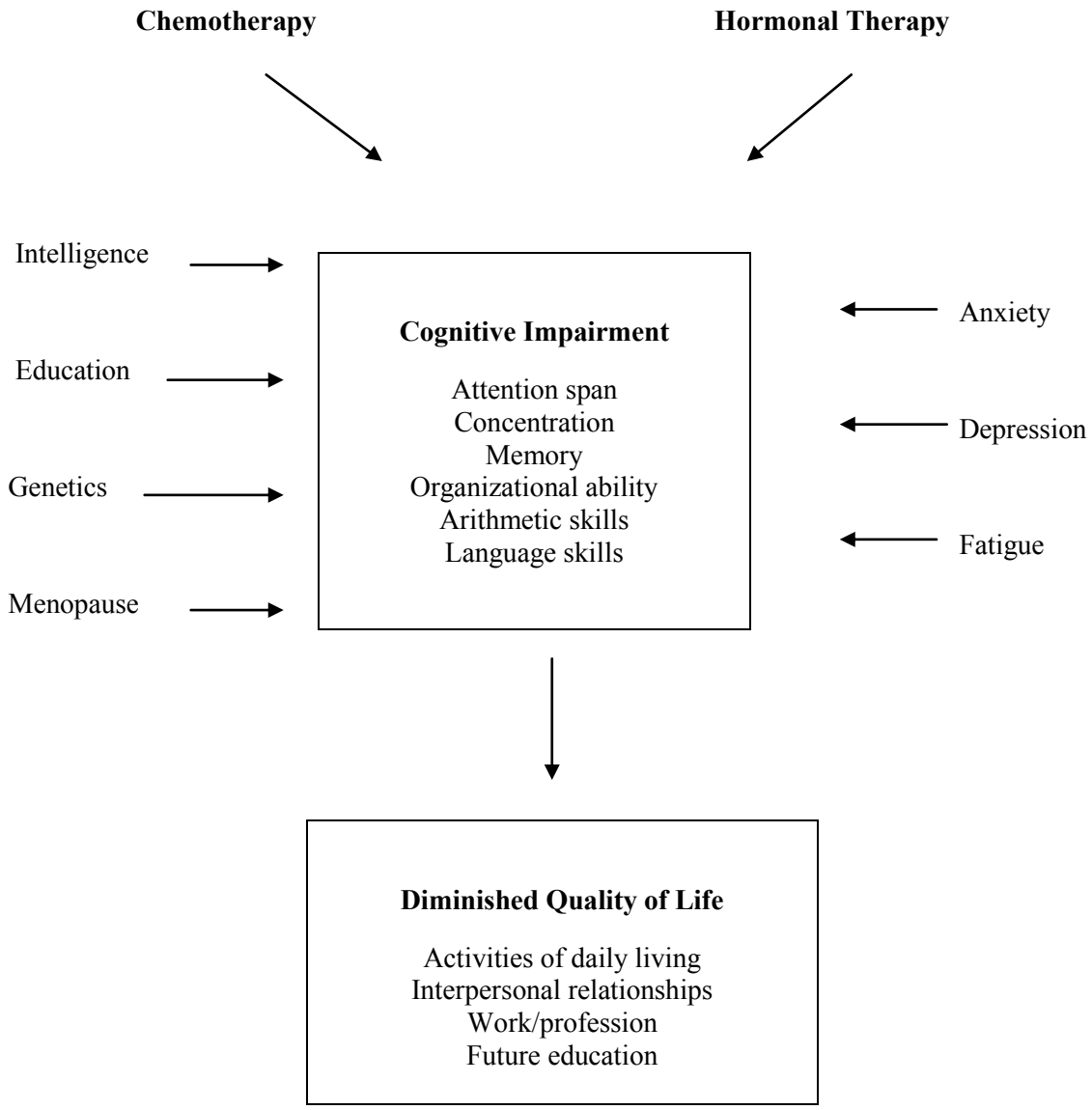
Appendices

Appendix: A

Potential Contributing Factors to Cognitive Function and Quality of Life



(Source: Olin, 2001, p. 616).

Appendix B

Skills Associated with the Various Cognitive Domains

1. Attention – enables a person to triage relevant inputs, thoughts and actions while ignoring those that distract or are irrelevant.

2. Concentration - ability to focus and sustain attention. Concentration and attention are often used synonymously.

3. Information processing speed – ability of the brain to rapidly process both simple and complex information.

4. Memory – ability to acquire, store and use new information, and is an outcome of learning. It is a way for the brain to process information that will be available for use at a later time. The most common types of memory are visual and verbal.

5. Language – incorporates oral and written communication, the process of which involves representing, comprehending and communicating symbolic information.

6. Executive function- higher order cognitive processes including cognitive flexibility, decision planning, regulation, judgement, feedback utilization and self-perception.

7. Visuospatial skill – ability to process and interpret visual information regarding where objects are situated in space.

8. Psychomotor function - motor performance such as speed, strength and co-ordination.

(Sources: Budson & Price, 2005; Cimprich, 1995; Jansen, Miaskowski, Dodd, & Dowling, 2005)

Appendix C:

Table C1

Sample Size Calculation Table

Number of time points	Effect Size	Sample size per group	Total Sample Size	Power
3	0.2	287	574	0.8
3	0.3	128	256	0.8
3	0.4	72	144	0.8
3	0.5	46	92	0.8
3	0.2	385	770	0.9
3	0.3	171	342	0.9
3	0.4	96	192	0.9
3	0.5	62	124	0.9
5	0.2	267	533	0.8
5	0.3	118	237	0.8
5	0.4	67	133	0.8
5	0.5	43	85	0.8
5	0.2	357	714	0.9
5	0.3	159	317	0.9
5	0.4	89	178	0.9
5	0.5	57	114	0.9

Source: Ghosh, S. (Ph.D., P.Stat.) Assistant Clinical Professor, Department of Oncology, University of Alberta and Research Scientist, Alberta Health Services - CancerControl Alberta (Personal communication June 2, 2010).

Appendix D

Table D1

Eastern Cooperative Oncology Group (ECOG)

Performance Status Scale

Grade	Description
0	Asymptomatic: Fully active, able to carry out all pre-disease performance without restriction.
1	Symptomatic, fully ambulatory: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, *e.g*., light housework, office work.
2	Symptomatic, in bed < 50% of the day: Ambulatory and capable of all self-care but unable to carry out work activities. Up and about more than 50% of waking hours.
3	Symptomatic, in bed > 50% of the day: Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Bedridden: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Source: Oken, M.M., et al. (1982). Toxicity and response criteria of the Eastern Cooperative Oncology Group. *American Journal of Clinical Oncology, 5*, 649-655.

Appendix E

HREB and ACREC Letters of Approval

Health Research Ethics Board

308 Campus Tower
University of Alberta, Edmonton, Alberta T6G 1K8
p.780.492.9724 (Biomedical Panel)
p.780.492.0302 (Health Panel)
p.780.492.0459
p.780.492.0839
f.780.492.7808

September 24, 2010

Dr. Karin Olson
Ms. Joanne Hewitt
Faculty of Nursing
University of Alberta

Dear Dr. Olson:

Re: Cognitive Dysfunction in non-Hodgkin's Lymphoma Patients Treated with Front-Line Chemotherapy

Thank you for submitting this application for reciprocal approval.

The Alberta Cancer Research Ethics Committee approved the above named protocol on August 25, 2010. They also approved the information letter and all associated documentation related to this application.

This letter serves as the official acknowledgment that this ACREC approval has been accepted by the University of Alberta and by its Health Research Ethics Board. Please note that the ACREC will remain your REB-of-record.

Yours sincerely,

Wendy M. Rodgers, PhD
Professor
Director, Human Research Protections Program
University of Alberta

Alberta Health Services

RECEIVED SEP 10, 2010

25 August 2010

Dr. Karin Olson
Associate Professor
Faculty of Nursing
University of Alberta

Dear Dr. Olson:

RE: 25438: Cognitive Dysfunction in non-Hodgkin's Lymphoma Patients treated with Front-Line Chemotherapy

Thank you for Joanne Hewitt's response to my correspondence dated 29 July 2010. I am pleased to grant approval to your participation in the above noted study on behalf of the Alberta Cancer Research Ethics Committee (ACREC). The following documents have been reviewed and approved as of 25 August 2010:

- Research of Minimal Risk Combined Protocol and Application Form (revised August 19, 2010)
- Protocol dated 5 July 2010 (including Appendices A – I)
- Participant Consent Form dated 15 July 2010
- Blood Sample Banking Consent Form dated 15 July 2010

Please note that this approval is based on the following conditions:

- a copy of the informed consent form must be given to each research subject and consent obtained prior to enrollment on the study;
- if there are any other changes to the protocol or consent form during the year, or if any serious adverse events to the treatment are found, a letter describing the changes/reactions must be forwarded to the ACREC together with an updated consent form;
- an Annual Renewal form must be submitted two months prior to the deadline date of 29 July 2011 (one year from date of the convened ACREC meeting), containing the information as per our annual renewal form;
- a Final Report must be submitted at the termination of the project.

The deliberations of the ACREC include all elements described in Section 50 of the Health Information Act, and this study was found to be in compliance with all the applicable requirements of the Act. The ACREC determined that consent will be obtained from study participants for disclosure of the health information to be used in the research.

The Alberta Cancer Research Ethics Committee complies with the following guidelines and regulations:

- Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans;
- Health Information Act which has been proclaimed on April 25, 2001 in Alberta;
- Health Canada, as defined in C.05 (Part C Division 5) of the Food And Drug Regulations-Amendment (Schedule No. 1024) and the Therapeutic Products Directorate Guidelines/ICH Harmonized Tripartite Guidelines-Good Clinical Practice: Consolidate Guidelines;
- National Institutes of Health-Code of Federal Regulations (USA); and
- Our institution has been approved by the Office for Human Research Protections in the United States.

Members of the ACREC who are named as investigators or co/sub-investigators in research studies do not participate in discussion related to, nor vote on, such studies when they are presented to the ACREC.

Please accept the Committee's best wishes for success in your research.

Sincerely,

Quincy Chu, MD
Acting Deputy Chair, Alberta Cancer Research Ethics Committee

/lg

cc: Joanne Hewitt
Clinical Research Unit, CCI
Caroline Shewchuk (Pharmacy – CCI)
NACTRC
OIPC

Alberta Cancer Research Ethics Committee 02 WCM, University of Alberta Hospital, 8440-112 Street, Edmonton AB T6G 2B7
Tel: (780) 407-3652/ (780) 407-1610 Email: Research.Ethics@albertahealthservices.ca

1. The membership of the Research Ethics Committee complies with the membership requirements for Research Ethics Boards defined in Part C Division 5 of the *Food and Drug Regulations*;
2. This Research Ethics Committee carries out its functions in a manner consistent with Good Clinical Practices; and
3. This Research Ethics Committee has reviewed and approved the clinical trial protocol and informed consent form for the trial which is to be conducted by the qualified investigator named above at the specified clinical trial site(s). This approval and the views of this Research Ethics Committee have been documented in writing.

Appendix F

Approved Study Consent Forms

Alberta Health Services

Cognitive Dysfunction in non-Hodgkin's Lymphoma Patients Treated with Front-Line Chemotherapy

(A study looking at changes in cognition (thinking ability) in patients with non-Hodgkin's lymphoma being treated with chemotherapy)

CONSENT FORM

This form is part of the process of informed consent. It is designed to explain this research study and what will happen to you if you choose to be in this study.

If you would like to know more about something mentioned in this consent form, or have any questions at anytime regarding this research study, please be sure to ask your doctor or nurse. Read this consent form carefully to make sure you understand all the information it provides. You will get a copy of this consent form to keep. You do not have to take part in this study and your care does not depend on whether or not you take part.

Your doctor has given us permission to ask you to be in this study.

This study is being conducted as part of the thesis requirements for a PhD degree in the Faculty of Nursing/Faculty of Graduate Studies and Research at the University of Alberta.

Your participation in this study is entirely voluntary. Please take your time to make your decision. It is recommended that you discuss with your friends and/or family about whether to participate in this study.

"WHY IS THIS STUDY BEING DONE?"

You are being asked to take part in this study because you have non-Hodgkin's lymphoma for which you will be receiving chemotherapy.

This study is being done because patients receiving chemotherapy often complain that they have problems with their cognitive function (cognitive dysfunction) (also referred to as "chemo brain", cognitive deficits or cognitive impairment). This means that they sometimes find they have problems with concentration, memory, learning, paying attention etc. that is a new concern or is different from their usual cognitive abilities.

Research into this problem has only recently been undertaken and as such not much is known about the causes, the types and/or severity of the changes in cognition that patients might experience, or the effect that it has on the patients' quality of life and daily activities. It is estimated about 20 to 25%

"HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?"

About 100 people will take part in this study at the CCI.

"WHAT WILL MY PARTICIPATION INVOLVE?"

If you take part in this study, you will have the following tests:

Name of Test	Time to complete (minutes)	Schedule of Testing		
		Baseline (before start of chemotherapy)	During Chemotherapy (before Cycle 4)	Follow-up (1, 6, & 12 months after end of chemotherapy)
FACT-Lym questionnaire (measures quality of life)	5 – 10	X	X	X
FACIT-F questionnaire (measures symptoms of fatigue)	Less than 5	X	X	X
FACT-Cog (measures how you would rate your cognitive function)	5 - 10	X	X	X
DASS questionnaire (measures symptoms of depression, anxiety, stress)	5	X	X	X
NAART reading test (a measure for estimating your pre-illness thinking ability)	10	X		
CogState Tests (tests to measure your cognitive function)	30	X	X	X
Blood sample (about 2 tablespoons) (for banking – see below)		X		1 month after end of chemotherapy

You will also be asked to provide some demographic information such as your highest level of education, whether you are right or left-handed, your ethnicity, and if you are a woman, your menopausal status. You may also be asked to provide some disease related information such as current medications, past medical history, and/or symptoms if this is not on your medical record.

The FACT-Lym, FACIT-F, FACT-Cog, and DASS are all standard self-report questionnaires that measure symptoms of quality of life, fatigue, your perceived cognitive function, depression, anxiety, and stress.

The CogState test is a computer based test battery designed to measure your cognitive function at baseline and to look for any changes (either better or worse) that occur over time. It has been reported to have been used without difficulty by people with various illnesses and of all ages, including those who may have had little or no previous computer experience. The researcher will be present at each testing time-point while you are completing these tests to provide guidance/instructions and answer any questions that you may have.

Sometimes when a person is diagnosed with an illness, his or her thinking ability may not be as good as it was when they were healthy. The NAART is a list of 35 words that you will be asked to read aloud in order to provide an estimate of what your thinking ability was like before you were diagnosed with lymphoma. You will only be asked to do this reading test once (before the start of your chemotherapy).

It is estimated that it will take approximately 1 hour to complete all of the testing required for the study at each time-point.

You will be asked to consider agreeing to provide blood samples to be banked (saved) to be used for future research looking at possible factors that may contribute to the development of cognitive changes related to chemotherapy. You will be provided with another consent form which you will be asked to review. If you would like to participate and agree that your blood samples may be stored for future research, you will be asked to sign that consent form.

"HOW LONG WILL I BE INVOLVED IN THE STUDY?"

You may be in this study for as long as 18 months.

"WHAT ARE THE SIDE EFFECTS?"

There are no potential risks anticipated as a result of participation in the study.

"WHAT ARE MY RESPONSIBILITIES?"

You must be willing to attend all scheduled study visits and undergo all of the procedures described above.

"WHAT ARE MY ALTERNATIVES?"

You may choose not to participate in this study. This will have no impact on the treatment for your lymphoma.

"ARE THERE ANY BENEFITS TO PARTICIPATING IN THIS STUDY?"

Participation in this study may or may not be of personal benefit to you. However, based on the results of this study, it is hoped that, in the long-term, patient care can be improved.

"CAN I WITHDRAW FROM THIS STUDY?"

Taking part in this study is voluntary; you may withdraw from the study at any time if you wish to do so. If you decide to stop participating in the study, we encourage you to talk to the study investigator or your doctor first.

Should you decide to withdraw from the study at any time, information collected on you up until that point would still be provided to the investigator/researcher responsible for overseeing the study.

"ARE THERE COSTS TO ME FOR TAKING PART IN THIS STUDY?"

It is not anticipated that you will need to come to the Cross Cancer Institute more often than if you were not part of this study; However, should it be necessary for you to come in at a time other than your regularly scheduled clinic appointment there may be additional costs to you for taking part in this study such as:

- parking
- transportation
- meals
- babysitting, etc.

"WILL MY PERSONAL INFORMATION BE KEPT CONFIDENTIAL?"

Identifiable health information will be collected from you and from your Provincial Electronic Health Record (NetCare) during this study. This information may be used by the researchers who are carrying out this study, and may be disclosed to others as described below. Any research proposal to use information that identifies you for a purpose other than this study must be approved in advance by the Alberta Cancer Research Ethics Committee.

Direct access to your identifiable health information collected for this study will be restricted to the researchers who are directly involved in this study except in the following circumstances:

Your identifiable health information may need to be inspected or copied from time to time for quality assurance (to make sure the information being used in the study is accurate) and for data analysis (to do statistical analysis that will not identify you). The following organizations may do this inspection:

- Alberta Cancer Research Ethics Committee, the institutional review board at this centre
- Members of the Regulatory/Audit team at the Cross Cancer Institute for quality assurance purposes

UNDERSTANDING OF PARTICIPANTS

I can refuse to take part or withdraw from this study at any time without jeopardizing my health care. If I continue to take part in the study, I will be kept informed of any important new developments and information learned after the time I gave my original consent.

I also give consent for the Principal Investigator and Alberta Health Services (the Custodian) to disclose identifiable health information, as per the Alberta Health Information Act, to the organizations mentioned on the previous pages.

I have read and understood all of the information in this consent form. I have asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review and discussion. My consent has not been forced or influenced in any way. I consent to participate in this research study. Upon signing this form I will receive a signed copy of the consent.

(PRINT NAMES CLEARLY)

_____	_____	_____
Name of Patient	Signature of Patient	Date
_____	_____	_____
Name of Person Obtaining Consent	Signature of Person Obtaining Consent	Date

Patient Study Number or Hospital Number: _____

Was the patient assisted during the consent process in one of the ways listed below?
□ Yes □ No

If yes, please check the relevant box and complete the signature space below:

□ The consent form was read to the patient, and the person signing below attests that the study was accurately explained to, and apparently understood by the patient.

□ The person signing below acted as a translator for the patient during the consent process.

_____	_____
Signature of person assisting In the consent discussion	Date

Please note: More information regarding the assistance provided during the consent process should be noted in the medical record for the patient if applicable.

I give permission for the research team to use my information collected in this study for future research studies provided that these additional studies receive approval from the appropriate ethics committee, and/or for educational purposes.

Signature of Research Participant: _____

Printed Name: _____

Date: _____

Alberta Health Services

Cognitive Dysfunction in non-Hodgkin's Lymphoma Patients Treated with Front-Line Chemotherapy

(A study looking at changes in cognition (thinking ability) in patients with non-Hodgkin's lymphoma being treated with chemotherapy)

BANKING OF BLOOD SAMPLE FOR FUTURE RESEARCH

This form is part of the process of informed consent. It is designed to explain what this research study is about and what will happen to your blood sample(s) if you choose to be in the study.

If you would like to know more about something mentioned in this form, or if you have any questions regarding this study, please be sure to ask your doctor or nurse. Read this form carefully to make sure you understand all the information it provides. You will get a copy of this form to keep. You do not have to take part in this study and your care does not depend on whether or not you take part.

Your doctor has given us permission to ask you to be in this study.

Your participation in this study is entirely voluntary. Please take your time to make your decision. It is recommended that you discuss with your friends and/or family about whether to participate in this study.

"WHAT IS BLOOD SAMPLE BANKING?"

Your blood will be put in a blood cell bank where it may be made available to investigators for future research projects.

"WHAT BLOOD SAMPLE IS BEING BANKED?"

You are being asked to take part in this study because you have non-Hodgkin's lymphoma for which you will be receiving chemotherapy and have agreed to participate in the research study titled: "Cognitive Dysfunction in non-Hodgkin's Lymphoma Patients Treated with Front-Line Chemotherapy". It is not known why some patients receiving chemotherapy will experience problems with cognitive dysfunction, while others do not. It may be possible that biological markers (for example, proteins or genes) may contribute to the development of this side effect. It is expected that more will become known about such potential biomarkers in the future including methods for testing for the presence or absence of them in the blood. As such, we are asking your permission to store part of your blood sample for future research. The hope is that we will

be able to learn more about what factors may contribute to the development of cognitive changes in patients receiving chemotherapy.

If you agree to participate in the blood banking portion of the study, a small blood sample (approximately 30 ml or 2 tablespoons) will be drawn at two time-points:

1) before the start of chemotherapy, and
2) 1 month after the end of chemotherapy.

"WHAT ARE THE RISKS OF GIVING A BLOOD SAMPLE FOR BANKING?"

A blood sample will be obtained at the same time as blood tests, which are required for your medical care. Therefore, there will be no additional risk of blood sampling. There is always a small risk of infection or bruising when a blood sample is collected from your vein. This risk is no greater than it would be for taking blood samples as part of your clinical care.

"WHAT ARE THE BENEFITS TO BANKING MY BLOOD SAMPLE?"

There will be no direct benefit to you from these studies and the results of these studies will not affect your treatment. The research that may be done with your sample(s) is not designed for you specifically. However, the knowledge gained may help us learn about, prevent or treat cancer or other conditions in the future.

"WHERE WILL MY BLOOD SAMPLE BE STORED?"

The samples and corresponding study data for patients on this study will be kept by the Alberta Health Services Cancer Care at the Cross Cancer Institute. Your sample that is collected for banking purposes will be stored in a secure area/storage.

"WHO CAN ACCESS MY BLOOD SAMPLE AND INFORMATION?"

Your sample will be available for researchers to use for future research. The researcher must provide the bank with an approval letter from a recognized research ethics committee. As well, treatment information, information collected as part of the main research study and/or other health information may be matched to your samples. None of the samples or information given pertaining to the sample will include your name; a number will identify all samples. Thus, none of these investigators will be able to identify you.

If required, your medical records pertaining to this study at the Cross Cancer Institute will be made available according to the Alberta Health Services policies and procedures to representatives of the following organizations:

- Alberta Cancer Research Ethics Committee, the institutional review board at this centre
- Members of the Regulatory/Audit team at the Cross Cancer Institute for quality assurance purposes

You will not be identified by name in any information otherwise released or in information resulting from this study when published.

"WILL I RECEIVE ANY OF THE RESULTS FROM THE RESEARCH CONDUCTED ON MY BLOOD SAMPLE?"

Reports about research done with your sample(s) will not be given to you or your doctor. These reports will not be put in your health records.

Sometimes sample(s) are used for genetic research (about diseases that are passed on in families). Even if your sample(s) are used for this kind of research, you will not be told about the results and these results will not be put in your health records.

Your sample(s) will be used only for research and will not be sold. The research done with your sample(s) may help to develop new products in the future, which may have monetary value, but you will not get paid.

"CAN I WITHDRAW MY BLOOD SAMPLE AT ANYTIME?"

The choice to let the researcher keep the sample(s) for future research is up to you. No matter what you decide to do, it will not affect your participation in this study. If you decide now that your sample(s) can be kept for research, you can change your mind at any time. Just contact the researcher or your doctor and let him or her know that you do not want your sample(s) used, and they will be destroyed. Otherwise, the sample(s) may be kept until they are used up, or until the researcher decides to destroy them.

"WHAT DO I NEED TO DO TO GIVE MY PERMISSION?"

Please read each sentence below and think about your choice. After reading each sentence, circle "yes" or "no". If you have any questions, please talk to your doctor or nurse. Remember, no matter what you decided to do about the storage and use of your sample(s), you can still participate in the study protocol titled "Cognitive Dysfunction in non-Hodgkin's Lymphoma Patients Treated with Front-Line Chemotherapy".

By signing this form, you are agreeing that:

1. Your blood sample may be kept by the researcher for use in future research to learn about, prevent, or treat cancer.

   YES NO

2. Your sample(s) may be used for research about other health problems (for example: diabetes, heart disease, etc).

   YES NO

"WHO DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?"

For information about your disease and/or research related injury/illness, you may contact the Investigator, Joanne Hewitt NP, PhD candidate at 780-432-8791 or the Principal Investigator/Thesis Supervisor, Karin Olson RN, PhD at 780492-6403 to answer any questions you have about this study.

If the investigator or the thesis supervisor have not been able to answer or resolve your questions and/or concerns about this study, or if you feel at any time that you have not been informed to your satisfaction about the risks, benefits, or alternatives to this study, or that you have been encouraged to continue in this study after you wanted to withdraw, you can call the Alberta Health Services Patient Concerns Department at 780-342-8080 or toll free at 1-877-753-2170

UNDERSTANDING OF PARTICIPANTS

I can refuse to take part or withdraw from this study at any time without jeopardizing my health care. If I continue to take part in the study, I will be kept informed of any important new developments and information learned after the time I gave my original consent.

I also give consent for the Principal Investigator and Alberta Health Services (the Custodian) to disclose identifiable health information, as per the Alberta Health Information Act, to the organizations mentioned on the previous pages.

I have read and understood all of the information in this consent form. I have asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review and discussion. My consent has not been forced or influenced in any way. I consent to participate in this research study. Upon signing this form I will receive a signed copy of the consent.

(PRINT NAMES CLEARLY)

_____	_____	_____
Name of Patient	Signature of Patient	Date
_____	_____	_____
Name of Person Obtaining Consent	Signature of Person Obtaining Consent	Date

Patient Study Number or Hospital Number: _____

Was the patient assisted during the consent process in one of the ways listed below?
□ Yes □ No

If yes, please check the relevant box and complete the signature space below:

□ The consent form was read to the patient, and the person signing below attests that the study was accurately explained to, and apparently understood by the patient.

□ The person signing below acted as a translator for the patient during the consent process.

_____	_____
Signature of person assisting In the consent discussion	Date

Please note: More information regarding the assistance provided during the consent process should be noted in the medical record for the patient if applicable.

Appendix G

Demographic, Disease and Treatment Data Collection Form

Data Collection Worksheet – Page 1

Name of Study: Cognitive Dysfunction in non-Hodgkin's Lymphoma Patients Treated with Front-Line Chemotherapy

Patient Study ID #:
Date consent signed:

Demographic Information

DOB	
Gender	**M** ☐ **F** ☐
Ethnicity	
Educational level (Highest attained)	
Handedness	**Right** ☐ **Left** ☐ **Ambidextrous** ☐
Post menopausal	**Yes** ☐ **If yes, natural** ☐ **or surgical** ☐ **No** ☐ **N/A** ☐

Lymphoma Information

Diagnosis	DLBCL ☐ Other (specify) ☐ FCL ☐ MCL ☐
Date of diagnosis	
Stage	I ☐ II ☐ III ☐ IV ☐ B symptoms Y ☐ N ☐
Prognostic Index Score	IPI ☐ Other (specify) ☐ FLIPI ☐ MIPI ☐

Chemotherapy Information

Start date	
End date	
# of cycles administered	
Dose reductions	Yes ☐ No ☐ If yes, which drugs
Premedications	Standard ☐ Other (specify) ☐

Data Collection Worksheet – Page 2 Patient Study ID #:

Name of Study: Cognitive Dysfunction in non-Hodgkin's Lymphoma Patients Treated with Front-Line Chemotherapy

Co morbidities None ☐

Concomitant Medications None ☐

*Timepoint	Medications
T1	
T2	No change ☐ Additions (list) Deletions (list)
T3	No change ☐ Additions (list) Deletions (list)
T4	No change ☐ Additions (list) Deletions (list)
T5	No change ☐ Additions (list) Deletions (list)

Hemoglobin Level

*Timepoint	Hemoglobin level (G/L)
T1	
T2	
T3	
T4	
T5	

*Timepoints: T1 – Baseline; T2 – During chemo (after cycle 3, before cycle 4); T3 – 1 month post end of chemo; T4 – 6 months post end of chemo; T5 – 12 months post end of chemo

Data Collection Worksheet – Page 3 Patient Study ID #:

Name of Study: Cognitive Dysfunction in non-Hodgkin's Lymphoma Patients Treated with Front-Line Chemotherapy

Symptoms

*Timepoint	Symptom	**NCIC grade**
T1		
T2		
T3		
T4		
T5		

Date Assessments Completed

	*T1	T2	T3	T4	T5
FACT-Lym					
FACT-F					
FACT-Cog					
DASS					
NAART35					
Cog-Stat					

Additional Comments

*Timepoints: T1 – Baseline; T2 – During chemo (after cycle 3, before cycle 4); T3 – 1 month post end of chemo; T4 – 6 months post end of chemo; T5 – 12 months post end of chemo

Appendix H

Depression Anxiety Stress Scales (DASS)

DASS21 *Name:* *Date:*

Please read each statement and circle a number 0, 1, 2 or 3 that indicates how much the statement applied to you *over the past week*. There are no right or wrong answers. Do not spend too much time on any statement.

The rating scale is as follows:

0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree, or a good part of time
3 Applied to me very much, or most of the time

1	I found it hard to wind down	0	1	2	3
2	I was aware of dryness of my mouth	0	1	2	3
3	I couldn't seem to experience any positive feeling at all	0	1	2	3
4	I experienced breathing difficulty (eg, excessively rapid breathing, breathlessness in the absence of physical exertion)	0	1	2	3
5	I found it difficult to work up the initiative to do things	0	1	2	3
6	I tended to over-react to situations	0	1	2	3
7	I experienced trembling (eg, in the hands)	0	1	2	3
8	I felt that I was using a lot of nervous energy	0	1	2	3
9	I was worried about situations in which I might panic and make a fool of myself	0	1	2	3
10	I felt that I had nothing to look forward to	0	1	2	3
11	I found myself getting agitated	0	1	2	3
12	I found it difficult to relax	0	1	2	3
13	I felt down-hearted and blue	0	1	2	3
14	I was intolerant of anything that kept me from getting on with what I was doing	0	1	2	3
15	I felt I was close to panic	0	1	2	3
16	I was unable to become enthusiastic about anything	0	1	2	3
17	I felt I wasn't worth much as a person	0	1	2	3
18	I felt that I was rather touchy	0	1	2	3
19	I was aware of the action of my heart in the absence of physical exertion (eg, sense of heart rate increase, heart missing a beat)	0	1	2	3
20	I felt scared without any good reason	0	1	2	3
21	I felt that life was meaningless	0	1	2	3

6.7 Appendix I

FACT-Lym, FACIT-Fatigue and FACT-COG Questionnaires

FACT-Lym (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-Lym (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
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	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-Lym (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
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
LEU1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
LYM1	I am bothered by itching	0	1	2	3	4
LYM2	I have trouble sleeping at night	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
Ga1	I have a loss of appetite	0	1	2	3	4
HS8	I have trouble concentrating	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU6	I worry that I might get new symptoms of my illness	0	1	2	3	4
LEU7	I feel isolated from others because of my illness or treatment	0	1	2	3	4
BRM9	I have emotional ups and downs	0	1	2	3	4
LEU4	Because of my illness, I have difficulty planning for the future	0	1	2	3	4

FACIT Fatigue Scale (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.

		Not at all	A little bit	Some-what	Quite a bit	Very much
H7	I feel fatigued	0	1	2	3	4
H12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

FACT-Cognitive Function (Version 3)

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

	PERCEIVED COGNITIVE IMPAIRMENTS	Never	About once a week	Two to three times a week	Nearly every day	Several times a day
CogA1	I have had trouble forming thoughts	0	1	2	3	4
CogA3	My thinking has been slow	0	1	2	3	4
CogC7	I have had trouble concentrating	0	1	2	3	4
CogM9	I have had trouble finding my way to a familiar place	0	1	2	3	4
CogM10	I have had trouble remembering where I put things, like my keys or my wallet	0	1	2	3	4
CogM12	I have had trouble remembering new information, like phone numbers or simple instructions	0	1	2	3	4
CogV13	I have had trouble recalling the name of an object while talking to someone	0	1	2	3	4
CogV15	I have had trouble finding the right word(s) to express myself	0	1	2	3	4
CogV16	I have used the wrong word when I referred to an object	0	1	2	3	4
CogV17b	I have had trouble saying what I mean in conversations with others	0	1	2	3	4
CogF19	I have walked into a room and forgotten what I meant to get or do there	0	1	2	3	4
CogF23	I have had to work really hard to pay attention or I would make a mistake	0	1	2	3	4
CogF24	I have forgotten names of people soon after being introduced	0	1	2	3	4

FACT-Cog (Version 3)

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

		Never	About once a week	Two to three times a week	Nearly every day	Several times a day
CogF25	My reactions in everyday situations have been slow	0	1	2	3	4
CogC31	I have had to work harder than usual to keep track of what I was doing	0	1	2	3	4
CogC32	My thinking has been slower than usual	0	1	2	3	4
CogC33a	I have had to work harder than usual to express myself clearly	0	1	2	3	4
CogC33c	I have had to use written lists more often than usual so I would not forget things	0	1	2	3	4
CogMT1	I have trouble keeping track of what I am doing if I am interrupted	0	1	2	3	4
CogMT2	I have trouble shifting back and forth between different activities that require thinking	0	1	2	3	4

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

	COMMENTS FROM OTHERS	Never	About once a week	Two to three times a week	Nearly every day	Several times a day
CogO1	Other people have told me I seemed to have trouble remembering information	0	1	2	3	4
CogO2	Other people have told me I seemed to have trouble speaking clearly	0	1	2	3	4
CogO3	Other people have told me I seemed to have trouble thinking clearly	0	1	2	3	4
CogO4	Other people have told me I seemed confused	0	1	2	3	4

FACT-Cog (Version 3)

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

	PERCEIVED COGNITIVE ABILITIES	Not at all	A little bit	Some-what	Quite a bit	Very much
Cog PCI	I have been able to concentrate	0	1	2	3	4
Cog PVI	I have been able to bring to mind words that I wanted to use while talking to someone	0	1	2	3	4
Cog PMI	I have been able to remember things, like where I left my keys or wallet	0	1	2	3	4
Cog PM2	I have been able to remember to do things, like take medicine or buy something I needed	0	1	2	3	4
Cog PFI	I am able to pay attention and keep track of what I am doing without extra effort	0	1	2	3	4
Cog PCH 1	My mind is as sharp as it has always been	0	1	2	3	4
Cog PCH 2	My memory is as good as it has always been	0	1	2	3	4
Cog PMT 1	I am able to shift back and forth between two activities that require thinking	0	1	2	3	4
Cog PMT 2	I am able to keep track of what I am doing, even if I am interrupted	0	1	2	3	4

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

	IMPACT ON QUALITY OF LIFE	Not at all	A little bit	Some-what	Quite a bit	Very much
CogQ35	I have been upset about these problems	0	1	2	3	4
CogQ37	These problems have interfered with my ability to work	0	1	2	3	4
CogQ38	These problems have interfered with my ability to do things I enjoy	0	1	2	3	4
CogQ41	These problems have interfered with the quality of my life	0	1	2	3	4

Appendix J

North American Adult Reading Test (NAART35)

Source: Strauss, E., Sherman, E.M.S., & Spreen, O. (2006). *A compendium of neuro-psychological tests. Administration, norms, and commentary* (3rd ed.). New York: Oxford University Press, pp.189 -200.

NAART 35

Sample Scoring Sheet

Page1

DEBRIS	HORS D'OEVRE
SIMILE	SIEVE
SUBTLE	HIATUS
BOUQUET	GAUCHE
COLONEL	ZEALOT
RAREFY	PARADIGM
GIST	FACADE
CORPS	

Page 2

CELLIST	CAVEAT
INDICT	LEVIATHAN
DETENTE	QUADRUPED
IMPUGN	SIDEREAL
AEON	ABSTEMIOUS
EPITOME	BEATIFY
REIFY	GAOLED
INDICES	DEMESNE
ASSIGNATE	SYNCOPE
TOPIARY	ENNUI

Instructions for NAART35

"I want you to read slowly down this list of words starting here (indicate 'debris') and continuing down this column and onto the next. When you have finished reading the words on the page, turn the page over and begin here" (indicate top of second page).

"After each word please wait until I say 'Next' before reading the next word"

I must warn you that there are many words that you probably won't recognize; in fact most people don't know them, so just guess at these, OK? Go ahead."

The examinee should be encourage to guess, and all responses should be reinforced ("good," "that's fine", etc.). The examinee may change a response if he or she wishes to do so but if more than one version is given, the examinee must decide on the final choice. No time limit is imposed.

SCORING

The use of a pronunciation guide and a tape recorder is recommended to facilitate scoring. Each incorrectly pronounced word counts as one error. Slight variations in pronunciation are acceptable when they are due to regional accents. The total number of errors is tabulated.

Pronunciation symbols follow Webster's dictionary.

Appendix K

CogState Academic Battery – Tests/Tasks Available

Source: CogState Website: http://www.cogstate.com/go/research

CogState Research

Fixed Response Mapping Task

Administration Time (in healthy volunteers): 10 seconds

Cognitive Domain Usually Measured: N/A

Task Description:

The Fixed Response Mapping Task does not have any outcome measures - it is simply a quick task that gets familiarizes users with the buttons needed for CogState's card-based tasks. It is always presented just before the first card task.

The pre-task on-screen instructions displays: "Practice pressing YES and NO"

Depending on the test battery, the choices may include the "D" or "K" buttons on the keyboard, the "left" or "right" mouse buttons, or external response buttons.

Once the subject presses the "D" button, the "left" mouse button or the left external response button, the word "NO" on the screen will flash indicating the key pressed corresponds to a "NO" response. When the subject presses the "K" button, the "right' mouse button or the right external response button, the word "YES" on the screen will flash, indicating the key pressed corresponds to a "YES" response. The subject is allowed to practice until they are confident before moving on to the card task by pressing the "ENTER".

Chase Test

Administration Time (in healthy volunteers): 0.5 Minute

Cognitive Domain Usually Measured: Visual Motor Function

Task Description:

The aim of this task is to introduce the subject to the rules of the Groton Maze tasks.

The pre-task on-screen instructions state: "Chase the Target". The test supervisor will read the full task instructions to the subject. To begin the task, the test supervisor or subject must press the "Enter" key. The subject will first complete a practice test.

The subject is shown a 10 x 10 grid of tiles on a computer touch screen.

The subject is asked to tap the blue tile in the top left corner of the grid with the stylus pen. As the target moves, the subject 'chases' it by tapping on the tiles one at a time. The subject cannot move diagonally and cannot skip a tile. If the subject makes a mistake, they must go back to the last correct tile.

The subject should be encouraged to move as quickly and accurately as possible. Once the test supervisor judges that the subject understands the rules, the subject is instructed to click on the "Finish" button in the upper left corner of the screen.

The subject is then asked to repeat the same task for a timed period of 30 seconds. The same rules apply as in the practice. The subject chases the target until the task stops.

Primary Outcome measures:

Unit of measurement: Moves per second

Description and interpretation of scores: The total number of correct moves made per second. (Higher score = better performance)

Groton Maze Learning Test

Administration Time (in healthy volunteers): 5 Minutes

Cognitive Domain Usually Measured: Executive Function / Spatial Problem Solving

Task Description:

The subject is shown a 10 x 10 grid of tiles on a computer touch screen. A 28-step pathway is hidden among these 100 possible locations. The start is indicated by the blue tile at the top left and the finish location is the tile with the red circles at the bottom right of the grid. The subject is instructed to move one step from the start location and then to continue, one tile at a time, toward the end (bottom right).

The subject moves by touching a tile next to their current location with the stylus. After each move is made, the computer indicates whether this is correct by revealing a green checkmark (i.e. this is the next step in the pathway), or incorrect by revealing a red cross (i.e. this is not the next step in the pathway, or the subject has broken a rule, see below). If a choice is incorrect (i.e. a red cross is revealed), the subject must touch the last correct location (i.e. the last green checkmark revealed) and then make a different tile choice to advance toward the end.

While moving through the hidden maze, the subject is required to adhere to two rules. Firstly, the subject cannot move diagonally or touch the same tile twice in succession. Secondly, the subject cannot move backwards along the pathway (e.g. move back to a location that displayed a green tick, but from which they have since moved on from).

If the subject chooses a tile that is not part of the hidden pathway, but the tile choice is within the rules, this is recorded as a different type of error (e.g. not a rule break). This could be due to chance (the first time through the maze) or due to misremembering the path on subsequent attempts.

The subject learns the 28-step pathway though the maze on the basis of this trial and error feedback. Once completed, they are returned to the start location and repeat the task, usually 4 more times, trying to remember the pathway they have just completed.

There are 20 well-matched alternate forms for this task, and these are selected in pseudo-random order to ensure that no subject will complete the same hidden path on any two different testing sessions throughout a study.

Primary Outcome measures:

Unit of measurement: Errors

Description and interpretation of scores: Total number of errors made in attempting to learn the same hidden pathway on five consecutive trials at a single session. (Lower score = better performance

Set-Shifting Task

Administration Time (in healthy volunteers): 5 Minutes

Cognitive Domain Usually Measured: Executive Function

Task Description:

The pre-task on-screen instructions ask: "Is this a target card?" The test supervisor will read full instructions to the subject from the test supervisor script. To begin the task, the test supervisor or subject must press the "Enter" key.

A playing card is presented in the center of the screen. At the start of this task, the subject literally has to guess whether the card is the 'target' or 'correct' card. The subject is being asked to determine whether the card contains a target stimulus dimension (a color or a number).

As the subject makes their guesses, the software provides feedback and will not display the next stimuli until a correct response has been made. For example, if the subject wants to guess that a card is correct he/she presses "Yes". If the guess is correct, the card will flip over. If the guess is incorrect, the subject will hear an error sound and the card will not flip over, indicating that the card does not contain the target stimulus dimension. In this case the subject would guess again (e.g. choose "No" to indicate that the card is 'incorrect'). In this way, the subject is taught that a specific dimension of the card (either a color or a number) is 'correct'.

When the subject has made their way through a set of cards, the 'target' or 'correct' stimulus dimension changes, either to the opposing example within the same dimension (eg, from red to black - intra-dimensional shift) or to a different dimension of the stimuli altogether (eg, from color to number - extra-dimensional shift). The subject is not told when these intra-dimensional or extra-dimensional 'set-shifts' occur, and they must re-learn the new target 'rule' to proceed through the task. There are multiple set-shifts within the task, and the order of these set-shifts is pseudo-randomized to create multiple alternate forms of the task.

The subject should be encouraged to work as quickly as they can and be as accurate as possible.

Primary Outcome measures:

Unit of measurement: Total number of errors

Description and interpretation of scores: Accuracy of performance; Total number of errors across five rounds. (Lower score = better performance)

Detection Task

Administration Time (in healthy volunteers): 2 Minutes

Cognitive Domain Usually Measured: Psychomotor Function / Speed of Processing

Task Description:

The pre-task on-screen instructions ask: "Has the card turned over?" The test supervisor will read full instructions to the subject from the test supervisor script.

To begin the task, the test supervisor or subject must press the "Enter" key.

A playing card is presented in the center of the screen.

The card will flip over so it is face up. As soon as it does, the subject must press the "Yes" key.

The card will go to the back of the pack and the subject must press the "Yes" key as soon as the next card flips over and so on. The subject will practice until he/she reaches the required number of responses, or until the practice period expires.

Then, on screen instructions for the real test are presented. The test supervisor or subject must press the "Enter" key to begin the real test.

The subject should be encouraged to work as quickly as he/she can and be as accurate as they can. For example, he/she should try not to press the "Yes" key before a card flips over. If the subject does this or does not respond to a card that has flipped over in time, he/she will hear an error sound.

Primary Outcome Measures:

Unit of measurement: Log10 milliseconds

Description and interpretation of scores: Speed of performance; mean of the log10 transformed reaction times for correct responses. (Lower score = better performance)

Identification Task

Administration Time (in healthy volunteers): 2 Minutes

Cognitive Domain Usually Measured: Visual Attention / Vigilance

Task Description:

The pre-task on-screen instructions ask: "Is the card red?" The test supervisor will read full instructions to the subject from the test supervisor script.

To begin the task, the test supervisor or subject must press the "Enter" key. A playing card is presented in the center of the screen.

The card will flip over so it is face up. As soon as it does this the subject must decide whether the card is red or not.

If it is red he/she should press "Yes", if it is not red he/she should press "No".

The subject will practice until they reach the required number of responses, or until the practice period expires.

Then, on screen instructions for the real test are presented. The test supervisor or subject must press the "Enter" key to begin the real test.

The subject should be encouraged to work as quickly as they can and be as accurate as he/she can. For example, the subject should try not to press either the "Yes" or "No" key before a card flips over. If he/she makes a mistake they will hear an error sound.

Primary Outcome measures:

Unit of measurement: Log10 milliseconds

Description and interpretation of scores: Speed of performance; mean of the log10 transformed reaction times for correct responses. (Lower score = better performance)

One Card Learning Task

Administration Time (in healthy volunteers): 5 Minutes

Cognitive Domain Usually Measured: Visual Learning & Memory

Task Description:

The pre-task on-screen instructions ask: "Have you seen this card before in this task?" The test supervisor will read full instructions to the subject from the test supervisor script.

To begin the task, the test supervisor or subject must press the "Enter" key. A playing card is presented in the center of the screen. As soon as it does the subject must decide whether or not the same card has been seen before in this task. Therefore the first answer is always "No".

Each time a card is revealed, the subject must decide whether he/she has been shown that card before in this task and respond by pressing the "Yes" or "No" key. If an incorrect response is given (e.g. "No" is pressed when a card has been presented before) an error noise is heard. Once the practice is complete (required number of responses or time out reached) the on-screen instructions and the test supervisor will tell the subject that the real test will now begin. The test supervisor or subject must press the "Enter" key to begin the real test.

The subject should be encouraged to work as quickly as he/she can and be as accurate as possible. For example, the subject should try not to press either the "Yes" or the "No" key before a card turns over, and the subject should try and remember all the cards that are presented in this task. If the subject makes a mistake he/she will hear an error sound.

Primary Outcome measures:

Unit of measurement: Arcsine proportion correct

Description and interpretation of scores: Accuracy of performance; arcsine transformation of the square root of the proportion of correct responses. (Higher score = better performance)

Continuous Paired Associate Learning Task

Administration Time (in healthy volunteers): 5 Minutes

Cognitive Domain Usually Measured: Visual Learning & Memory

Task Description:

Stage 1

The pre-task on-screen instructions ask: "In what locations do these pictures belong"

In this task, the subject must learn and remember the pictures hidden beneath different locations on the screen. The subject must tap the target on the central location to begin. As each picture to be learned is revealed, the subject must tap each location and remember where the picture was located.

Stage 2

The pre-task on-screen instructions ask: "In what locations do these pictures belong"

Now the same pictures will be presented in the center of the screen, and the subject must tap on the peripheral location where that picture previously appeared.

Primary Outcome measures:

Unit of measurement: Total errors

Description and interpretation of scores: Accuracy of performance; total number of errors across five rounds. (Lower score = better performance)

Groton Maze Learning Test - Delayed Recall

Administration Time (in healthy volunteers): 1 Minute

Cognitive Domain Usually Measured: Visual Learning & Memory

Task Description:

The 10 x 10 grid of tiles is shown again on the computer screen. The subject is asked to reproduce the pathway that he/she learned at the start of the CogState battery. The subject should start at the top left tile and try to remember the path to the end of the maze at the bottom right. The subject completes this delayed recall trial once.

Primary Outcome measures:

Unit of measurement: Total errors

Description and interpretation of scores: Accuracy of performance; total number of errors after a delay. (Lower score = better performance)

International Shopping List Task

Administration Time (in healthy volunteers): 5 Minutes

Cognitive Domain Usually Measured: Verbal Learning & Memory

Task Description:

The phrase "Shopping List Learning" is displayed on screen. The pre-task on-screen instructions tell the test supervisor to start this task with the screen facing the supervisor so that the subject cannot see the screen.

Trial 1
The subject is told by the test supervisor: "In this task, I am going to read you a shopping list. I would like you to remember as many items from this list as possible. Are you ready to start?"

To begin, the test supervisor presses the "ENTER" key. The test supervisor reads the list of words as they appear on the computer screen at a rate of one word every two seconds.

When the test supervisor has read all the words they ask: "Tell me as many of the items on the shopping list as you can remember?"

As the subject recalls each word, the test supervisor clicks the appropriate button on the screen with the stylus or mouse.

If the subject says a word that was not on the list, the test supervisor will click "Other Word". If the subject repeats a word, the test supervisor will click the corresponding button as many times as the word is said. If a button is clicked by mistake, the test supervisor can select "Undo Last" and then continue recording.

Trial 2 (and subsequent trials)
When the subject cannot recall any more items then the test supervisor instructs, "I am going to read you that same shopping list. Try and remember as many items as you can. Are you ready to start?

The entire word list is read again, in the same order as it was read previously. To begin, the test supervisor presses the "ENTER" key and reads the list of words as they appear on the computer screen at a rate of one word every two seconds. When the test supervisor has read all words they ask: "Now what were the items on the shopping list?"

Again, the test supervisor notes the items recalled by the subject by clicking/touching the corresponding button on screen with the stylus or mouse.
In the standard version of this test, 3 learning trials are presented following this format.

The difficultly level of this task can be adjusted by presenting less or more words. The list of words can be anywhere from 2 to 16.

Primary Outcome measures:

Unit of measurement: Number of correct responses

Description and interpretation of scores: Total number of correct responses made in remembering the list on three consecutive trials at a single session. (Higher score = better performance)

International Shopping List Task - Delayed Recall

Administration Time (in healthy volunteers): 2 Minutes

Cognitive Domain Usually Measured: Verbal Learning & Memory

Task Description:

In this task the individual is not shown anything. They are asked: "Now we are going to go back to the shopping list I read to you earlier. I need you to try and remember the items on this list and tell me what they were. Are you ready to start?"

The test supervisor presses the "ENTER" key to begin and instructs the subject "Tell me as many of the items on the shopping list as you can remember." They then note all of the items recalled by the subject by clicking/touching the corresponding button on screen with the stylus or mouse.

Primary Outcome measures:

Unit of measurement: Number of correct responses

Description and interpretation of scores: Total number of correct responses made in remembering the list after a delay. (Higher score = better performance)

One Back Task

Administration Time (in healthy volunteers): 2 Minutes

Cognitive Domain Usually Measured: Attention / Working Memory

Task Description:

The pre-task on-screen instructions ask: "Is the previous card the same?" The test supervisor will read the task instructions from the script. To begin the task, the test supervisor or subject must press the "Enter" key.

A playing card is presented face up in the center of the screen. The subject must decide as each card is presented whether it is identical to the one just before. Therefore the first answer is always "No". If the face up card is identical to the one presented immediately before it, the subject should press the "Yes" key, if it is not the same the subject should press the "No" key. The card in the center will go to the back of the pack revealing the next card. As soon as it does the subject must decide whether or not it is the same as the card he/she has just seen.

The subject will practice until they reach the required number of responses, or until the practice period expires.

Then, on screen instructions for the real test are presented. The test supervisor or subject must press the "Enter" key to begin the real test.

The subject should be encouraged to work as quickly as he/she can and be as accurate as possible. For example, the subject should try not to press either "Yes" or "No" key before a card turns over. If the subject makes a mistake he/she will hear an error sound.

Primary Outcome measures:

Unit of measurement: Arcsine proportion correct

Description and interpretation of scores: Accuracy of performance; arcsine transformation of the square root of the proportion of correct responses. (Higher score = better performance)

Two Back Task

Administration Time (in healthy volunteers): 2 Minutes

Cognitive Domain Usually Measured: Attention / Working Memory

Task Description:

The pre-task on-screen instructions ask "IS THE CARD THE SAME AS THAT SHOWN TWO CARDS AGO?" The test supervisor will read the task instructions from the script. To begin the task, the test supervisor or subject must press the "Enter" key.

A playing card is presented face up in the center of the screen. The subject must decide as each card is presented whether it is identical to the one just before. Therefore the first two answers are always "No". If the face up card is identical to the one presented two cards previously, the subject should press the "Yes" key, if it is not the subject should press the "No" key. The card in the center will go to the back of the pack revealing the next card. As soon as it does the subject must decide whether or not it is the same as the card they saw two cards previously.

The subject will practice until he/she reaches the required number of responses, or until the practice period expires.

Then, on screen instructions for the real test are presented. The test supervisor or subject must press the "Enter" key to begin the real test.

The subject should be encouraged to work as quickly as he/she can and be as accurate as possible. For example, the subject should try not to press either "Yes" or "No" key before a card turns over. If the subject makes a mistake he/she will hear an error sound.

Primary Outcome measures:

Unit of measurement: Arcsine proportion correct

Description and interpretation of scores: Accuracy of performance; arcsine transformation of the square root of the proportion of correct responses. (Higher score = better performance)

Social-Emotional Cognition Task

Administration Time (in healthy volunteers): 7 Minutes

Cognitive Domain Usually Measured: Social Cognition

Task Description:

The pre-task on-screen instructions ask, "Tap the odd one out". The test supervisor will read the task instructions from the script.

In this task, the subject will see a number of pictures on the screen. One of these pictures will be different to the others in some way. The subject must decide which one of the pictures is different then tap that picture as quickly as they can.

The subject should be encouraged to work as quickly and as accurately as they can after each set of pictures appears.

Primary Outcome measures:

Unit of measurement: Arcsine proportion correct

Description and interpretation of scores: Accuracy of performance; arcsine transformation of the square root of the proportion of correct responses. (Higher score = better performance)