Investigating Cognitive/Affective/Sleep Disturbance Symptoms in Patients Receiving High-Dose Interleukin-2 Therapy

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Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Nursing in the Graduate School of Duke University

2018
ABSTRACT

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Abstract

Patients undergoing intensive treatments for life-limiting chronic illnesses such as cancer often experience severe cognitive, affective, and sleep disturbance symptoms. Immunotherapies such as high-dose Interleukin-2 (IL-2) can result in severe alterations in cognition, affect, and sleep. These alterations not only prevent patients from receiving their full course of treatment but also severely impact the quality of life of patients and their care partners. A mixed-method case study approach was used to investigate the trajectory of these symptoms from three key informants (the patient receiving IL-2, the care partner, and the primary nurse) in ten IL-2 cases over up to four treatment hospitalizations. Quantitative measurement scores and qualitative reports of symptom change were compiled to understand the symptom trajectory within and across treatment hospitalizations.

This dissertation includes a systematic literature review in Chapter 2 that highlights the lack of trajectory analysis surrounding cognitive, affective, and sleep disturbance symptoms in patients undergoing IL-2, as well as the gravity and impact that these symptoms have on patients and their families. Chapter 3 features the study team’s evaluation of methods using a case study approach to collect quantitative and qualitative data from one patient, care partner, and primary nurse as a case triad to examine cognitive, affective, and sleep disturbance symptoms one patient diagnosed
with MRCC experienced during one hospitalization for IL-2 treatment, and this case served as the foundation for the larger study. Chapters 4 and 5 synthesized data from case informants in the larger study and described the trajectory of cognitive symptoms and affective and sleep disturbance symptoms, respectively, that patients receiving IL-2 therapy for renal cell carcinoma experienced within and across hospitalizations.

Cognitive, affective, and sleep disturbance symptoms are often synergistic and interdependent. Of these symptoms, fatigue and anxiety were the most frequently reported, worsening with each subsequent dose of IL-2, suggesting a cumulative dosing effect. Interventions should be uniquely designed to target patients receiving IL-2, care partners, nurses, and the healthcare team with the aim of reducing commonly reported yet severely incapacitating symptoms. A reduction in these symptoms can reduce other cognitive, affective, and sleep disturbance symptoms, improving the patient’s overall symptom trajectory experience.
Dedication

This dissertation is in memory of Balroop Kaur Mann, lovingly known as “Aunt Nina,” who passed away on February 2, 2005, from esophageal cancer. Thank you for your positive influence, and showing me how to be passionate, strong, and independent. You are remembered and deeply loved each day.

“In a gentle way, you can shake the world.” – Mahatma Ghandi
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1. Introduction

Patients undergoing intensive treatments for life-limiting, chronic illnesses such as cancer often experience severe cognitive, affective, and sleep disturbance symptoms. Alterations in cognition, affect, and sleep can have major effects on patients diagnosed with cancer who are receiving aggressive treatment (Bower et al., 2011; Mielcarek, Nowicka-Sauer, & Kozaka, 2016), and oftentimes, a standardized protocol to assess patients for these symptoms is not in place (Asher & Myers, 2015). Altered cognition includes symptoms related to concentration, attention, short-term memory, confusion, mental fatigue, executive functioning, abstraction, language, basic arithmetic, and orientation (McDonald, Flashman, & Saykin, 2002; The American Psychiatric Textbook of Neuropsychiatry, 1999; Vaughan, Agner, & Clinchot, 1997). Affective symptoms include psychosocial symptoms such as mood alterations, depression, anxiety, and suicidal ideation (Mavroukakis, Muehlbauer, White, & Schwartzentruber, 2001; Muehlbauer & White, 1998; Myint, Schwarz, Steinbusch, & Leonard, 2009; The American Psychiatric Textbook of Neuropsychiatry, 1999). Sleep disturbance symptoms include insomnia (initial, middle, delayed) and hypersomnia, and are prevalent in the cancer population (Absolon et al., 2014).

Understanding the trajectory of cognitive, affective, and sleep disturbance symptoms allows researchers to identify the temporal presentation of symptoms and
their trajectory of change during and after treatment. Insight into the temporal relationship of symptoms allows researchers to develop interventions to ameliorate symptoms and thus improve treatment adherence, remission rates, and quality of life.

To understand these common but often overlooked symptoms, the research team conducted a study of patients receiving (IL-2) therapy for metastatic renal cell carcinoma (MRCC) as an example and explanatory case. Trajectory analysis is the most powerful way to deconstruct symptom changes associated with cyclic dosing therapy such as IL-2 therapy because symptom responses are often cumulative and intensify over time (Dutcher et al., 2014). Cognitive, affective, and sleep disturbance symptoms can be interdependent and appear in unique clusters for each patient. A detailed analysis of symptom groups across the treatment trajectory (within and across hospitalizations) enables researchers to identify patterns in symptom appearance, intensity, and interdependence (Henly, Wyman, & Findorff, 2011).

### 1.1 Cognitive Symptoms

Even though nearly all patients receiving IL-2 therapy experience alterations in cognition during treatment (Fyfe et al., 1995), no recent research has focused on this area. However, a number of older studies identified specific cognitive symptoms in patients receiving high-dose IL-2 (Atkins et al., 1999; Fyfe et al., 1995; Rosenberg et al., 1994) such as alterations in mental status, confusion, somnolence, seizures, and fatigue.
Up to 80% of patients receiving IL-2 experience alterations in mental status, more than one-fourth experience moderate to severe cognitive symptoms (Fyfe et al., 1995), and approximately one-third experience confusion (Atkins et al., 1999; Gitlitz, Hoffman, Moldawer, Beldegrun, & Figlin, 2001; Kilbourn, Fonseca, Trissel, & Griffith, 2000). Seizures in patients receiving IL-2 are thought to be related to the cytokine storm initiated by immunotherapy; however, published literature (Stone & DeAngelis, 2016) does not document the prevalence of this treatment-related side effect. Although these articles date back to the mid- to late-1990s, the treatment protocol (e.g. dose sequence, hospitalizations) has not changed since 1992, the year the Food and Drug Administration approved high-dose IL-2 for the treatment of MRCC (and melanoma) (Stanford Hospital & Clinics, 2011).

In other cancer cohorts, the prevalence of treatment-related cognitive alterations is high. In the breast cancer population, researchers have reported that up to 60% of patients experience changes in cognition (attention, memory, concentration) after receiving treatment (Ahles, Root, & Ryan, 2012). Cancer-related fatigue has been reported in 60% to 90% of cancer patients (Mohandas, Jaganathan, Mani, Ayyar, & Rohini Thevi, 2017; Reilly et al., 2013). The cognitive symptom trajectory (i.e. how symptoms change from IL-2 dose to dose, how symptoms change from treatment
hospitalization to hospitalization, and which symptoms co-occur with cognitive symptoms) is unclear.

### 1.2 Affective Symptoms

Affective symptoms are prevalent in patients receiving IL-2 therapy and include depression, anxiety, and mood swings. Research describing affective symptoms in this population is limited. Researchers theorize that affective symptoms are related to increased pro-inflammatory cytokines (Musselman et al., 2013). Musselman et al. measured depressive symptoms over consecutive hospitalizations in patients receiving IL-2 therapy and reported a significant increase in depressive symptoms with each hospitalization, which peaked by the third treatment hospitalization. Capuron et al. (2002) measured depressive symptoms at baseline, one week after, and one month after IL-2 treatment and found significantly increased depressive symptoms at both the one-week and one-month follow-up appointments (Capuron et al., 2002). These findings indicate that patients receiving IL-2 therapy experience residual depressive symptoms. Internet-based list-serves that give patients a platform in which to discuss their experiences also describe affective symptoms beyond depression (American Cancer Society, 2015a). Reports on these list-serves suggest that patients receiving IL-2 therapy experience far more affective symptoms than previous studies have reported, and these symptoms warrant further investigation.
In other cancer cohorts, treatment-related affective symptoms were also prevalent and persisted well after treatment ended. In the breast cancer population, researchers identified depressive symptoms in patients who were five years out from treatment, which highlights the potential for prolonged negative effects (Maass, Roorda, Berendsen, Verhaak, & de Bock, 2015). Researchers who conducted a systematic review of treatment-related symptoms in cancer patients reported that 35% of patients receiving treatment experienced depression and 42% experienced anxiety (Reilly et al., 2013). Knowledge about the intersection of depressive symptoms with other affective symptoms is limited.

1.3 Sleep Disturbance Symptoms

Sleep disturbance symptoms exist concurrently with cognitive and affective symptom alterations. The study team was unable to identify any peer-reviewed studies investigating sleep disturbance symptoms in patients receiving IL-2. However, researchers have found that nearly 50% of all cancer patients experience sleep disturbance symptoms, the most prevalent of which is insomnia (Reilly et al., 2013). Similar to reports of affective symptoms, patients receiving IL-2 therapy have reported severe changes in sleep patterns on patient list-serves. This finding is consistent with high rates of reported sleep disturbance in other cancer cohorts (Absolon et al., 2014; Graci, 2005). Alterations in sleep patterns were found to exacerbate the cognitive
symptoms that breast cancer patients experience (Caplette-Gingras, Savard, Savard, & Ivers, 2013). Researchers identified a positive correlation between Interleukin-6, a pro-inflammatory cytokine, and fluctuations in sleep patterns in a group of women diagnosed with ovarian cancer (Clevenger et al., 2012). Increases in cytokines might contribute to hypersomnia and mood alterations. Collectively, researchers have demonstrated that cognitive, affective, and sleep disturbance symptoms are multifaceted, interdependent, and should be studied together (Caplette-Gingras et al., 2013; Clevenger et al., 2012).

Figure 1 depicts the reported symptom domains that patients receiving IL-2 experience and the negative outcomes associated with these symptoms. As shown, cognitive, affective, and sleep disturbance symptoms are often interdependent and synergistic. For example, increased sleep disturbance symptoms can result in increased cognitive and affective symptoms. More importantly, increased symptoms can result in treatment ending early, which can ultimately result in other negative symptoms.
Figure 1: IL-2 treatment-related symptom domains and negative outcomes

See Chapter 2 for a literature review describing what is known about IL-2-induced cognitive, affective, and sleep disturbance symptoms.

1.4 High-Dose Interleukin-2 Therapy

IL-2, a cytokine-based immunotherapy, is administered as a high-dose infusion to patients with metastatic disease to stimulate their immune systems to fight off cancerous cells (American Cancer Society, 2010) and place patients in remission. Patients with stage III and IV clear cell MRCC are treated with IL-2 therapy after undergoing a partial or total nephrectomy. IL-2 therapy is one of the few treatments available for patients with metastatic disease that has progressed subsequent to prior therapy (National Cancer Institute, 2013a). Stage III renal cell carcinoma is defined as cancer extending into the renal vein, vena cava, or outside the kidney to nearby lymph nodes, whereas stage IV renal cell carcinoma is defined as cancer extending beyond the
Gerota’s fascia or to distant locations (American Cancer Society, 2015b). In 2017, the National Cancer Institute estimated 63,990 new cases and 14,400 deaths secondary to kidney cancer (National Cancer Institute, 2017). However, statistics specifically related to MRCC are not available. Despite severe symptoms and side effects, 14% of MRCC patients show a partial response to IL-2 therapy and 8% achieve complete remission (Action to Cure Kidney Cancer, 2010; Eisenhauer et al., 2009). Given the intense symptom response associated with IL-2 therapy, it is understandable why many patients do not complete therapy. However, IL-2 is the only treatment option available for MRCC patients with a clear cell histology that offers them any hope of remission (Hawkins et al., 2012).

IL-2 therapy is routinely administered across four treatment hospitalizations. Each treatment hospitalization lasts approximately one week, followed by a two-week recovery period. During these hospitalizations, the patient receives up to 14 IL-2 doses administered every eight hours over five days. While complete treatment with IL-2 should include 14 doses for each of the four hospitalizations, one study reported that only about 35% of patients receiving IL-2 were admitted for all four hospitalizations (Musselman et al., 2013), and within each hospitalization, rarely do patients receiving IL-2 tolerate the maximum 14 doses. Researchers and clinicians hypothesize that patients who receive more doses have better disease response (Payne et al., 2014), yet worsening
symptoms prevent patients from completing the complete treatment regimen. Patients can become symptomatic with alterations in cognition, affect, and sleep after completing their first dose of IL-2 (Stanford Hospital & Clinics, 2011). Additionally, cognitive, affective, and sleep disturbance symptoms can change within and across hospitalizations for IL-2 therapy (Musselman et al., 2013). Thus far, limited published literature exists surrounding the exploration of cognitive, affective, and sleep disturbance symptoms that contribute to patients ending treatment early. A better understanding of this symptom trajectory could lead to a critical opportunity to improve treatment efficacy. While many of the side effects (e.g. cardiotoxicity, capillary leak syndrome, etc.) related to IL-2 therapy are managed with medications, cognitive, affective, and sleep disturbance symptoms continue to be overlooked by clinicians and researchers.

1.5 Case Study Approach

Case study research methodology originated in the social sciences and has been used by scientists seeking to understand complex, multifaceted research phenomena in their real-life contexts (Amerson, 2011; Anthony & Jack, 2009; Cronin, 2014; Crowe et al., 2011). This naturalistic methodological approach is beneficial when examining a phenomenon with unclear boundaries (Amerson, 2011; Crowe et al., 2011) that make the case difficult to disentangle from its context (McGloin, 2008; Yin, 2014). A holistic,
comprehensive approach to understanding the perceptions and experiences of people surrounding the phenomenon proves insightful (Swanborn, 2010) and might provide important information about the patient’s IL-2 treatment experience. A case study approach allows for the understanding of complex and dynamic processes (Zainal, 2007) through the analysis of data collected from multiple perspectives and contexts (Amerson, 2011). Multiple data collection methods (e.g., interviews, standardized measures, journal entries) provide comprehensive data that are essential to understanding the case (McGloin, 2008). Collecting data from multiple data sources is particularly beneficial because the patient receiving IL-2 therapy may not be aware of the symptoms he or she is experiencing because of their intensity. Similarly, because of the complex symptomatology experienced by patients receiving IL-2 therapy, researchers need to study cases from as many sources as possible to understand the IL-2 symptom experience.

Care partners are a necessary component of evaluating symptoms related to the aggressive treatment. Not only are care partners integral to the case, but they are also routinely required to stay with the patient receiving IL-2 during hospitalizations. Care partners assist patients with their ongoing needs. During the patient’s hospitalization, the care partner is also integral in observing and reporting worsening and changing symptoms and making sure the patient stays safe and does not cause harm to
themselves during acute changes such as alterations in mental status. Typically the care partner is a family member or close friend who has committed to caring for the patient at home, as well as in the hospital setting (Frambes, Given, Lehto, Sikorskii, & Wyatt, 2017). Care partners are familiar with the patient’s regular behavior and demeanor, so they are able to recognize when their loved one deviates from baseline. The care partner provides valuable insight into behavior changes of the patient receiving IL-2 (Roberto, McCann, & Blieszner, 2013) and often plays a large role in decision making, communication, and symptom management (Frambes et al., 2017; Laidsaar-Powell et al., 2017). Care partners who know the patient well can provide valuable information that can aid in the detection of symptoms as well as necessary interventions.

1.6 Trajectory Science

Health trajectory is defined as an individual’s physical, social, and mental state over time (Clevenger et al., 2012; Roberto et al., 2013). Historically, health trajectories were thought to be linear; however, researchers now know that health is a dynamic state on the illness-wellness continuum, influenced by many factors (e.g. intrinsic and extrinsic factors). Much of the research surrounding trajectory science aims to improve patient illness and symptom trajectories, which will ultimately improve patient outcomes. Understanding health trajectories allows providers, nurses, patients, and care
partners to personalize care based on the patient’s specific needs at a particular point in time along his/her health trajectory (Clevenger et al., 2012).

Trajectory science emphasizes person-centered research and longitudinal research methods to capture the patient’s experience (Henly et al., 2011; Roberto et al., 2013) over his/her lifespan or continuum of care, oscillating between wellness and illness (Amerson, 2011). Trajectory research has become a large focus in the nursing field (Henly et al., 2011), particularly in oncology nursing. Recent cancer studies have placed weight on gaining insight into factors affecting the cancer illness trajectory. Identifying accelerations in symptom and illness trajectories allows clinicians to design appropriate patient- and family-centered interventions (Anthony & Jack, 2009). Trajectory science has a broad scope extending beyond the study of symptoms and illness, and paints a holistic patient picture for the provider and researcher, allowing appropriate interventions to be developed and applied.

1.7 Theoretical Framework

The theory of symptom management (Linder, 2010; Smith & Liehr, 2014b) is the foundation of the theoretical model in this dissertation, as it leads to a holistic understanding of the patient’s symptom experience, symptom management, and symptom outcomes within the nursing science domains of person, environment, and health and illness (Smith & Liehr, 2014b). The concepts of symptom trajectory and the
inclusion of the care partner are not included in the theory of symptom management but are incorporated into the study team’s model because of their essential roles in understanding the IL-2 case (See Figure 2).

The theory of symptom management encompasses concepts central to nursing science such as looking at the inherent traits that the patient and care partner have that could impact the patient’s symptom experience. This model views the nursing science domains of environment and health/illness as permeable in that there is a complex interplay between the two in the way that they influence patients’ symptom experiences (Smith & Liehr, 2014b). The framework also incorporates feedback loops, as patients’ symptom experiences are dynamic, and their needs evolve over time. For example, as shown in one feedback loop, affective symptoms (frequency, severity, duration) impact the environment and outcomes such as quality of life (QOL), and similarly, the environment and QOL affect the severity, frequency, and duration of affective symptoms.

The treatment trajectory is an essential aspect of each IL-2 case, where IL-2 doses can have a cumulative effect on patients receiving IL-2, and past events can influence present outcomes (Dutcher et al., 2014). Many patients receiving IL-2 experience acute cognitive, affective, and sleep disturbance symptoms over the course of their treatment. These symptoms wax and wane depending on which treatment hospitalization the
patient is undergoing, the number of doses received, and previous toxicities. Therefore, the IL-2 study model (See Figure 2) includes the treatment trajectory as an essential component of the IL-2 symptom model.

The model in Figure 2 also includes person-related traits from the theory of symptom management such as demographic (e.g. socioeconomic status, gender, age), psychological, sociological, and physiological variables. These traits influence the patient’s perception of his/her symptoms, ultimately impacting the patient’s symptom experience.

The theory of symptom management views the nursing science domains of environment and health/illness as permeable, where elements from these domains can similarly influence the patient’s symptom experience. Environment-related factors include the patient’s physical environment (inpatient hospital unit), social environment (care partner at the bedside), and cultural environment (beliefs, values, religion). Health and illness factors include the number of IL-2 cycles received, the number of IL-2 doses received, and risk factors such as previous drug-related toxicities.

During IL-2 therapy, the patient’s care partner remains at the bedside and oftentimes is very engaged in assessing, reporting, and managing the patient’s symptoms. Because of their level of involvement in the patient’s care, the care partner and nurse also influence the patient’s symptom experience.
Finally, the IL-2 case study uses the feedback loop, a key concept in the theory of symptom management to adapt as the patients’ symptom experience is dynamic and evolves over time. As new symptoms arise, the role of the patient, care partner, and nurse change, as do management strategies and outcome expectations.

Figure 2: IL-2 case study framework: symptom management model

1.7.1 Symptom Experience for Patients Receiving High-Dose IL-2 for MRCC

The high-dose IL-2 model depicts the symptom experience along the treatment trajectory where the patient is central to his or her symptom experience, as shown in Figure 2. The serrated lines surrounding each symptom domain (cognitive, affective,
sleep) signify how intertwined these symptoms are and therefore how difficult they are to tease apart, leading to a convoluted symptom experience for the patient.

Effective symptom management can include a number of strategies, such as complementary and alternative approaches (Henneghan & Harrison, 2015; Huebner et al., 2014), stress management techniques (Aguado Loi et al., 2012), exercise, and pharmacologic interventions (Repka & Hayward, 2015). As the far right area of the IL-2 treatment trajectory indicates, the patient receiving IL-2, the care partner, and the nurse are central to the symptom management model, each having an equal hand in symptom assessment and management. The solid line that surrounds the “person” domain signifies that these patient, care partner, and nurse traits are intrinsic and likely will remain stable; however, they can still influence symptom management. The outer circle contains the potential positive outcomes on a big picture level that the patient and care partner can experience if symptoms are managed properly.

1.8 Purpose

The purpose of this dissertation is to describe the trajectory of cognitive, affective, and sleep disturbance symptoms in patients receiving high-dose IL-2 therapy. This study will address six aims in the following chapters:

- Aim 1 (Chapter 1): Position the problem in the larger context of symptom science.
• Aim 2 (Chapter 2): Conduct a systematic integrative review of the literature on IL-2-induced cognitive and affective symptoms.

• Aim 3 (Chapter 3): Investigate one case (patient receiving IL-2, care partner, and primary nurse) during one hospitalization for IL-2 therapy to evaluate the feasibility of the proposed research methods to generate knowledge surrounding the IL-2 symptom trajectory.

• Aim 4 (Chapter 4): Describe the trajectory of IL-2-induced cognitive symptoms in ten patients receiving IL-2 therapy using a mixed-method case study approach.

• Aim 5 (Chapter 5): Describe the trajectory of IL-2-induced affective and sleep disturbance symptoms in ten patients receiving IL-2 therapy using a mixed-method case study approach.

• Aim 6 (Chapter 6): Propose future directions of research and discuss implications for nursing research and nursing practice.
2. Cognitive and Affective Symptoms Experienced by Cancer Patients Receiving High-Dose Intravenous Interleukin-2 Therapy: An Integrative Literature Review

2.1 Background

Alterations in cognitive and affective functioning are among the most challenging side effects experienced by 80% of patients with metastatic melanoma (MM) and metastatic renal cell carcinoma (RCC) undergoing high-dose Interleukin-2 (IL-2) therapy (Fyfe et al., 1995). Altered cognition includes changes in concentration, attention, short-term memory, confusion, mental fatigue, executive functioning, abstraction, language, basic arithmetic and orientation (McDonald et al., 2002; The American Psychiatric Textbook of Neuropsychiatry, 1999; Vaughan et al., 1997), whereas affective symptoms include mood alterations, depression, anxiety, psychosis, hallucinations, aggression, suicide ideation and coma (Mavroukakis et al., 2001; Muehlbauer & White, 1998; Myint et al., 2009; The American Psychiatric Textbook of Neuropsychiatry, 1999). Severe cognitive/affective symptoms may result in early termination of IL-2 therapy, preventing the patient from receiving a therapeutic dose, decreasing the quality of life for patients and their informal caregivers. Furthermore, these cognitive and affective symptoms are seemingly difficult for providers to manage. In some patients, cognitive and affective symptoms continue throughout the remainder of their life (Myint et al., 2009). Because nurses are routinely assessing patients, and
therefore can quickly identify acute changes, educating nurses in addition to family members could be beneficial in assessing for and reporting alterations in cognition and affect. Early detection of cognitive/affective symptoms will allow for all care providers to intervene earlier, potentially reducing stress and anxiety in patients and their family members, while also allowing patients to receive more therapy.

The cognitive/affective symptoms experienced by IL-2 patients are largely understudied, yet they have a profound negative impact on patients, families and providers (Sparber & Biller-Sparber, 1993). Furthermore, many of the symptoms patients and their family members describe, have not been measured and disseminated in published literature. One patient described his experience with depression and anxiety:

On Monday, I became extremely depressed and felt a lot of panic. Panic in breathing, and in the efficacy of the treatment. I spent the day unable to think about anything but that, and it was a pretty dark day. Tuesday was more of the same with a few more brain cells firing on different things but still worry and panic.”...” Though I had read about the side effects of IL-2, I saw more the physical side effects and didn't really consider the mental ones. I am here to tell you that they are AS DEBILITATING as the physical ones and not to be underestimated (Ejneary, 2011).

In 2015, the National Cancer Institute estimated 73,870 new diagnoses and 9,940 deaths secondary to melanoma ("SEER Stat Fact Sheets: Melanoma of the Skin," 2015), and 61,560 new cases and 14,080 deaths secondary to kidney cancer ("SEER Stat Fact Sheets: Kidney and Renal Pelvis Cancer," 2015). The U.S. Food and Drug Administration approved the use of IL-2 in cancer patients in 1992 (National Cancer Institute, 2013b).
Patients with MM and metastatic RCC are treated with high-dose IL-2 therapy when surgery, chemotherapy and radiation therapy have been ineffective for those with stage III and IV disease. IL-2, a cytokine based immunotherapy, is given to patients with metastatic disease to stimulate their immune systems to fight off cancerous cells (American Cancer Society, 2010), and is one of the few treatments available for these patients (National Cancer Institute, 2013b). IL-2 is a therapy shown to be beneficial specifically for clear cell RCC patients with metastatic disease, where 94% of clear cell RCC patients have carbonic anhydrase IX, a RCC marker associated with better IL-2 outcomes (Petrulio, DeRafфеle, & Kaufman, 2007). When IL-2 is administered in high-dose, intravenous form, patients experience severe side effects (American Cancer Society, 2010; Atkins et al., 1999; Fyfe et al., 1995; Gitlitz et al., 2001; Guleria et al., 1994; MacFarlane et al., 1995; Petrella et al., 2007; Pockaj, Topalian, Steinberg, White, & Rosenberg, 1993; Rosenberg et al., 1994; White et al., 1994). Thus far, the long-term impact of IL-2 treatments on cognition and affect has not been thoroughly described. Depression has been measured a month after the cessation of IL-2 therapy (Capuron et al., 2002); yet, longitudinal studies of symptoms following treatment are absent in published literature. Several studies have identified cognitive (fatigue (Atkins et al., 2002; Atkins et al., 1999; Tarhini, Kirkwood, Gooding, Cai, & Agarwala, 2007), confusion or disorientation (Atkins et al., 1999; Rosenberg et al., 1994), seizures (Fyfe et al., 1995;
Gitlitz et al., 2001), mental status changes (Fyfe et al., 1995)), and affective (depression (Capuron et al., 2002; Musselman et al., 2013), hallucinations (Gitlitz et al., 2001), coma (Atkins et al., 1999; Fyfe et al., 1995; Rosenberg et al., 1994)) symptoms. These studies grade the severity of these symptoms; however, absent from the literature are descriptions of when and how these symptoms present, and how they change over time. Despite severe symptoms and side effects, 33% of MM patients have some response to IL-2 treatment and 15% of MM patients show a complete response with no detectable metastases after treatment (Eisenhauer et al., 2009; Petrella et al., 2007). In RCC, 14% of patients show some response and 8% have a complete response (Action to Cure Kidney Cancer, 2010; Eisenhauer et al., 2009). Therefore, it is important to understand the depth and breadth of cognitive/affective symptoms to help patients, families and providers manage these symptoms so the patient might complete the full course of therapy.

High-dose IL-2 is defined as 600,000-720,000 International Units/kilogram (IU/kg), which is administered intravenously over 15 minutes, every eight hours for a maximum of 14 consecutive doses; these 14 doses comprise one of up to four treatment cycles (Atkins et al., 1999). Despite the benefits of IL-2, managing the side effects of this treatment continues to pose a challenge for patients, family members and providers. One patient explained:

There was extreme mental craziness...I couldn't sleep, I paced the floor over and over, my brain was fried - even with sleep medication the dreams I had were just
terrifying. I wasn’t vocal enough with the medical staff about the things I was experiencing either. I was disoriented - and bewildered (Tabekat, 2011).

These quotes from patients and families highlight the importance of uncovering and understanding the wide array of cognitive and affective symptoms that patients receiving high-dose IL-2 therapy experience.

2.2 Objective

The purpose of this literature review is to describe what is known about IL-2—induced cognitive/affective symptoms, their prevalence and level of severity, and synthesize findings to determine areas for future research to address the challenges experienced by patients, family members and providers resulting from these symptoms. Patients receiving IL-2 therapy might tolerate more treatment, attain better response rates, and achieve better quality of life if life-threatening side effects are managed or reduced. This literature review describes the patient experience when undergoing high-dose IL-2, and the pathophysiology leading to these changes.

2.3 Methods

PubMed was used to identify relevant literature describing IL-2—induced cognitive/affective symptoms. Table 1 depicts the search filters, search term combinations, and manuscripts returned for each search. Results were limited to articles published after 1992, the year the Food and Drug Administration first approved IL-2 for cancer treatment.
Table 1: Summary of the database employed, search filters, search term combinations, and manuscript returned for each search

<table>
<thead>
<tr>
<th>Database</th>
<th>Search Filters</th>
<th>Search Terms</th>
<th>Articles Returned</th>
</tr>
</thead>
<tbody>
<tr>
<td>PubMed</td>
<td>Years: 1992-2015, Human, Adult (19+ yrs), Subject: Cancer</td>
<td>“Interleukin-2” AND “Depression” AND “Cancer”</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“IL-2” AND “Depression” AND “Cancer”</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“Interleukin-2” AND “Cognitive” AND “Cancer”</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“Interleukin-2” AND “Neurologic” AND “Cancer”</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“Interleukin-2” AND “Behavioral”</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“Interleukin-2” AND “Anxiety” AND “Cancer”</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“Interleukin-2” AND “Psychological” AND “Cancer”</td>
<td>13</td>
</tr>
</tbody>
</table>

Abbreviations: IL-2, Interleukin-2; Yrs, Years.

The 113 search results from PubMed were imported into EndNote® X6 and 38 duplicates were removed. The titles and abstracts of the 75 remaining manuscripts were reviewed, and reasons for exclusion are shown in Figure 3. The bibliographic snowball technique was used to locate five additional manuscripts for inclusion (Greenhalgh & Peacock, 2005). The 20 remaining manuscripts along with the five additional manuscripts were reviewed in full text. Studies of cancers other than melanoma and RCC were excluded because standard of care dictates that IL-2 is only effective in treating patients with these specific cancers. Nine manuscripts were retained that met inclusion criteria for the review.
Figure 3: Preferred reporting items for systematic reviews and meta-analyses flow chart of elimination process

The Matrix Method (Garrard, 2014) was used to extract the nine manuscripts into a spreadsheet with the following headings: author(s), article title/journal, side effects related to IL-2 administration, definition of concepts, measures, sample, methods, strengths/weaknesses, findings, and suggested areas of future research. A synthesis of each symptom experienced by patients receiving IL-2 is presented by characteristic, severity and prevalence.
Many of the cognitive side effects reported in this literature review were graded on toxicity. The term “toxicity” refers to the level of side effect severity, and is graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events scale (National Cancer Institute, 2010). The NCI grades symptom severity on a scale of 1-5; grade 1 represents “mild” side effects, grade 2 represents “moderate” requiring intervention, grade 3 represents “severe” requiring medical treatment, grade 4 represents “life-threatening” side effects resulting in hospitalization or hospice care, and grade 5 represents “death” (National Cancer Institute, 2010).

2.4 Results

This section begins with an overview of patient demographics, attrition and prior treatments reported in empirical articles, followed by an overview of cognitive and affective symptoms experienced by patients receiving high-dose IL-2 therapy. Results associated with cognitive symptoms are in Table 2. Table 3 provides detail on each manuscript.
### Table 2: Cognitive symptom severity and prevalence

<table>
<thead>
<tr>
<th>Construct</th>
<th>Symptom</th>
<th>Severity and Prevalence$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All Grades</td>
</tr>
<tr>
<td>Cognitive</td>
<td>Alterations in Mental Status</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>Confusion</td>
<td>30-35%</td>
</tr>
<tr>
<td></td>
<td>Somnolence</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>Seizure</td>
<td>1-2%</td>
</tr>
<tr>
<td></td>
<td>Fatigue and/or delirium</td>
<td>81%</td>
</tr>
</tbody>
</table>

Abbreviations: NR, Not Reported.

1: Grading using the National Cancer Institute Common Terminology Criteria for Adverse Events scale.
Table 3: Study methods: individual extraction of each manuscript

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Title</th>
<th>Year</th>
<th>Sample Size</th>
<th>Strengths &amp; Weaknesses</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atkins MB, Lotze MT, Dutcher JP, et al</td>
<td>High-Dose Recombinant Interleukin-2 Therapy for Patients with Metastatic Melanoma: Analysis of 270 Patients Treated Between 1985 and 1993</td>
<td>1999</td>
<td>N = 270</td>
<td>Strength = large sample size; Weakness = 8 different protocols in 22 different treatment centers decreasing internal reliability, also varying IV IL-2 doses received by pts</td>
<td>Retrospective study, inability to control for variables</td>
</tr>
<tr>
<td>Capuron L, Ravaud A, Neveu PJ, Miller AH, Maes M, Dantzer R</td>
<td>Association between decreased serum tryptophan concentrations and depressive symptoms in cancer patients undergoing cytokine therapy</td>
<td>2002</td>
<td>N = 16</td>
<td>Weakness = small sample size, different treatment protocols, international study (France)</td>
<td>Subcutaneous and IV IL-2 in sample</td>
</tr>
<tr>
<td>Fyfe G, Fisher RI, Rosenberg SA, et al</td>
<td>Result of Treatment of 255 Patients with Metastatic Renal Cell Carcinoma Who Received High-Dose Recombinant Interleukin-2 Therapy</td>
<td>1995</td>
<td>N = 255</td>
<td>Strength = large sample size; Weakness = different doses, 7 phase 2 trials and 21 treatment facilities</td>
<td>Retrospective, inconsistency in treatment dose, and facility</td>
</tr>
<tr>
<td>Gitlitz BJ, Hoffman DMJ, Moldawer N, et al</td>
<td>Treatment of Metastatic Renal Cell Carcinoma with High-Dose Bolus Interleukin-2 in a Non-Intensive Care Unit: An Analysis of 124 Consecutively Treated Patients</td>
<td>2001</td>
<td>N = 124</td>
<td>Strength = all patients received same dose, one facility, grade 3 + 4 toxicities stated</td>
<td>N/A</td>
</tr>
<tr>
<td>Mavroukakis SA, Muehlbauer PM, White RL, Jr., et al</td>
<td>Clinical Pathways for Managing Patients Receiving Interleukin 2</td>
<td>2001</td>
<td>N/A, Clinical pathway</td>
<td>Strength = holistic approaches to IL-2 management</td>
<td>Not a research study</td>
</tr>
<tr>
<td>Musselman D, Royster EB, Wang M, Long Q, Trimble LM, Mann TK, Graciaa DS, McNutt MD, Auyeung NS, Oliver L, Lawson DH, Miller AH</td>
<td>The impact of escitalopram on IL-2-induced neuroendocrine, immune, and behavioral changes in patients with malignant melanoma: preliminary findings</td>
<td>2013</td>
<td>N = 20</td>
<td>Strength = prospective, randomized control trial, one clinical site, strong internal reliability and validity; Weakness = small sample size</td>
<td>Sample size</td>
</tr>
<tr>
<td>Rosenberg SA, Yang JC, Topalian SL, et al</td>
<td>Treatment of 283 Consecutive Patients With Metastatic Melanoma or Renal Cell Carcinoma Using High-Dose Bolus Interleukin 2</td>
<td>1994</td>
<td>N = 283</td>
<td>Strength = prospective, large sample size, all treated with same IL-2 regimen in same location, using same measurement scales; strong internal reliability and validity</td>
<td>N/A</td>
</tr>
<tr>
<td>Sparber AG, Biller-Sparber K</td>
<td>Immunotherapy and neuropsychiatric toxicity. Nursing clinical management consideration.</td>
<td>1993</td>
<td>N/A, Clinical pathway</td>
<td>Strength = Clinical overview of neurotoxic symptoms</td>
<td>Not a research study</td>
</tr>
<tr>
<td>Tarhini AA, Kirkwood JM, Gooding WE, Cai C, Agawala SS</td>
<td>Durable complete responses with high-dose bolus interleukin-2 in patients with metastatic melanoma who have experienced progression after biochemotherapy</td>
<td>2007</td>
<td>N = 26</td>
<td>Strength = prospective, phase II trial, carried out on one inpatient unit with same protocols; Weakness = small sample size</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Abbreviations: IL-2, Interleukin-2; IV, Intravenous; N, Number; N/A, Not applicable; Pts, Patients.
2.4.1 Demographics, Attrition, and Treatment

The median ages of patients enrolled in the high-dose IL-2 studies ranged from 42 to 52 years, with the youngest reported age of 18 years, and oldest reported age of 74 years. Large attrition rates were seen in patients receiving high-dose IL-2; only a small fraction of the population was able to receive all four cycles of IL-2 therapy. Attrition rates reported were: 7% to 58% of patients stopped treatment after cycle 1, 29% to 52% after cycle 2, 3% to 20% after cycle 3, and only 3% to 35% of patients completed the maximum four cycles of high-dose IL-2. One study reported the reasons for attrition as: patient’s choice, major depression, brain metastases/disease progression or cardiac event (Musselman et al., 2013). Patients received re-evaluation scans after cycle 2 of high-dose IL-2 therapy, which might explain the high attrition rate after this cycle. Patients who had disease progression (development of brain metastases or development of additional lesions) were ineligible to receive additional cycles of IL-2. Interleukin-2 therapy is contraindicated for patients with brain metastases because increased fluid in the brain is thought to place patients at a higher risk for brain lesion hemorrhage due to the increase in intracranial pressure (Schwartz, Stover, & Dutcher, 2002).

Six articles reported the treatments that patients received prior to high-dose IL-2 therapy (Atkins et al., 1999; Fyfe et al., 1995; Gitlitz et al., 2001; Musselman et al., 2013; Rosenberg et al., 1994; Tarhini et al., 2007). Of these six studies, two studies only enrolled
RCC patients (Fyfe et al., 1995; Gitlitz et al., 2001), two studies only enrolled melanoma patients (Atkins et al., 1999; Tarhini et al., 2007), and two studies enrolled both melanoma and RCC patients (Musselman et al., 2013; Rosenberg et al., 1994). Table 4 shows the treatments that melanoma and RCC patients received prior to high-dose IL-2 therapy. Over 75% of patients diagnosed with RCC had a nephrectomy. Nearly all patients with melanoma had surgery prior to treatment. Furthermore, many patients had multiple treatments prior to IL-2 therapy, including chemotherapy, previous immunotherapy, hormone therapy, radiation and/or surgery.
Table 4: Treatments received by patients prior to high-dose IL-2 therapy

<table>
<thead>
<tr>
<th>Disease</th>
<th>Treatment</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Melanoma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chemotherapy</td>
<td>23-100%</td>
</tr>
<tr>
<td></td>
<td>Hormone Therapy</td>
<td>1-3%</td>
</tr>
<tr>
<td></td>
<td>Immunotherapy</td>
<td>30-35%</td>
</tr>
<tr>
<td></td>
<td>Radiation</td>
<td>13-35%</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
<td>96%</td>
</tr>
<tr>
<td><strong>Melanoma and RCC&lt;sup&gt;2&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brain Radiosurgery</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Immunotherapy</td>
<td>40%</td>
</tr>
<tr>
<td><strong>RCC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nephrectomy</td>
<td>74-94%</td>
</tr>
<tr>
<td></td>
<td>Immunotherapy</td>
<td>4-18%</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy</td>
<td>3-7%</td>
</tr>
<tr>
<td></td>
<td>Hormone</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Radiation</td>
<td>10%</td>
</tr>
</tbody>
</table>

Abbreviations: IL-2, Interleukin-2; RCC, Renal Cell Carcinoma.

1: Percentages may add up to more than 100% because many patients receive multiple therapies prior to IL-2.
2: This study did not differentiate between melanoma and RCC patients when reporting demographic variables.

### 2.4.2 Cognitive Symptoms

Alterations in cognition, which include a wide array of symptoms, such as lethargy, confusion, inability to focus and sleep insufficiency are among the most challenging IL-2 side effects for patients and family members to experience and for
providers to manage (Mavroukakis et al., 2001; Muehlbauer & White, 1998; Poust, Woolery, & Green, 2013). “Cognitive fatigue” is a phrase encompassing the cognitive symptoms of IL-2, such as the symptoms listed above in addition to confusion, decreased memory, and decreased attention span. The exact etiology of IL-2—induced cognitive alterations has yet to be determined. There are two theories related to altered cognition in patients receiving high-dose IL-2 therapy: 1) changes in brain matter (white and grey matter) in chemotherapy patients (Poust et al., 2013) might be similar in IL-2 patients because IL-2 crosses the blood-brain barrier, and 2) alterations in cognition are related to fluid overload in the brain or cerebral edema, creating alterations in brain functioning (Muehlbauer & White, 1998), possibly related to capillary leak syndrome.

Fyfe and colleagues found that approximately 80% of patients experienced alterations in mental status, with more than one-fourth of IL-2 patients experiencing moderate to severe cognitive alterations (Fyfe et al., 1995). Approximately a third of IL-2 patients experienced confusion (Atkins et al., 1999; Gitlitz et al., 2001; Kilbourn et al., 2000), or severe neurotoxicity (Gitlitz et al., 2001). Seizures in IL-2 patients are rare, although it is not clear if seizures that have been reported are related to a previous history of seizures or the development of brain metastases (Fyfe et al., 1995; Gitlitz et al., 2001).
It is difficult to determine what percentage of IL-2 patients are predisposed to cognitive alterations; however, cognitive fatigue impacts nearly 80% of patients receiving IL-2 (Fyfe et al., 1995). Fortunately, grade 3 and 4 cognitive side effects impact slightly less than 25% of IL-2 patients (Fyfe et al., 1995). The low percentage of reported grade 3 and 4 cognitive side effects might be because patients who experienced severe symptoms removed themselves from therapy prior to receiving the full course of treatment.

2.4.3 Affective Symptoms

Affective symptoms, such as mood alterations, depression, anxiety, aggression, hallucinations and coma are difficult for patients and family members to adapt to (Mavroukakis et al., 2001; Muehlbauer & White, 1998; Poust et al., 2013). Gitlitz and colleagues reported that nearly 35% of IL-2 patients experience “hallucinations or significant neurotoxicity” but we do not know the severity, or which affective symptoms the research team defined as neurotoxic (Gitlitz et al., 2001). The symptom of depression has been reported; however, descriptions of other affective symptoms were only found on patient list-serves designed to allow patients and their family members to discuss their disease and treatments over the internet (American Cancer Society, 2015a). Musselman and colleagues (2013) measured depression with the Hamilton Depression Scale, while Capuron and colleagues (2002) used the Montgomery-Asberg Depression
Rating Scale to assess for depression. The 21-item Hamilton Depression Scale rates scores 0-6 as “normal”, 7-17 as “mild” depression, 18-24 as “moderate” depression, and scores equal to or greater than 25 as “severe” depression (Hamilton, 1960). The 10-item Montgomery-Asberg Depression Rating Scale grades scores under 10 as “normal” and scores greater than 30 as “severe” depression (Cusin, Yang, Yeung, & Fava, 2010). Both scales measure various dimensions of depressive symptomatology, but these researchers did not report other affective symptoms described by patients and families, such as anxiety and hallucinations.

Musselman and colleagues (2013) conducted a randomized control trial where they sought to determine if the prophylactic use of escitalopram, a selective serotonin reuptake inhibitor, reduced the level of depression in patients receiving the intervention drug. They measured depression over consecutive cycles of IL-2 and reported a significant increase in depression with each cycle, reaching a maximum level of depression in the cycle 3. Mean scores on the Hamilton Depression Scale increased by 10 points (Musselman et al., 2013). Capuron and colleagues (2002) measured depression at baseline, one-week and one-month after IL-2 therapy, and found an increase in depression scores at one-week after therapy, with a significant increase at the one-month time point.
The etiology of changes in affective symptoms from IL-2, such as depression, mood swings, fear and tearfulness is unknown; however, pro-inflammatory cytokines that are associated with mood regulation, such as adrenocorticotropic hormone, cortisol levels and Interleukin-6 are theorized to be a contributing factor to depression levels (Musselman et al., 2013). It is hypothesized that cytokine-induced depression might be related to a disruption in the metabolism of serotonin (Capuron et al., 2002), a neurotransmitter associated with mood stability and quality sleep (National Institutes of Health, 2014). Tryptophan is an essential amino acid precursor necessary for the synthesis of serotonin (National Institutes of Health, 2014). Capuron and colleagues found that a decrease in peripheral serum tryptophan levels was significantly associated with decreased appetite, pessimistic thoughts, suicide ideation and decreased concentration (Capuron et al., 2002). Because tryptophan is not produced by the body, it must be acquired through food (National Institutes of Health, 2014), potentially contributing to a depression cycle related to loss of appetite and inevitably lower tryptophan levels (Capuron et al., 2002).

In summary, two studies measured depression (Capuron et al., 2002; Musselman et al., 2013), and one study reported hallucinations (Gitlitz et al., 2001). Hallucinations were reported with signs of severe neurotoxicity; therefore, we were unable to distinguish the percentage of patients who experienced hallucinations as opposed to
other affective symptoms. Reports and descriptions of other affective symptoms have been neglected in the published literature thus far. The few studies measuring affective symptoms in the high-dose IL-2 population were underpowered. Sample sizes for studies were 20 (Musselman et al., 2013), and 16 participants (Capuron et al., 2002), respectively.

2.4.4 Limitation of Existing Evidence

Within the reviewed literature, there was a wide array of studies varying in sample size, research design, reliability, and validity. Table 3 depicts an analysis of study methods for each manuscript used for this review. Of the nine manuscripts, seven contained empirical data (Atkins et al., 1999; Capuron et al., 2002; Fyfe et al., 1995; Gitlitz et al., 2001; Musselman et al., 2013; Rosenberg et al., 1994; Tarhini et al., 2007), while two contained general information about IL-2 for patients, families and providers (Mavroukakis et al., 2001; Sparber & Biller-Sparber, 1993), giving insight into known side effects and their clinical management. Of the seven empirical studies, five used prospective methods (Capuron et al., 2002; Gitlitz et al., 2001; Musselman et al., 2013; Rosenberg et al., 1994; Tarhini et al., 2007), and two used retrospective methods (Atkins et al., 1999; Fyfe et al., 1995). Studies were conducted in as few as one site and as many as 22 research centers (multi-center research). Sample sizes ranged from 16 to 283 participants. Five of the studies used the NCI toxicity scale for rating cognitive symptom
severity (Atkins et al., 1999; Fyfe et al., 1995; Gitlitz et al., 2001; Rosenberg et al., 1994; Tarhini et al., 2007), while the two studies describing affective symptoms used depression scales to report symptom severity (Capuron et al., 2002; Musselman et al., 2013).

Although studies reporting cognitive symptoms enrolled between 124 and 283 participants, internal reliability was low because of the varying treatment centers and treatment protocols, particularly in retrospective studies. Only two studies evaluated affective symptoms, and sample sizes for these studies were small, ranging from 16 to 20 participants (Capuron et al., 2002; Musselman et al., 2013). There was a lack of standardization when assessing and screening for cognitive and affective symptoms in the high-dose IL-2 population. There appears to be a lack of consistency in the way cognitive/affective symptoms were reported, leading us to believe that each clinical facility may screen differently for cognitive/affective symptoms. Without an understanding of cognitive/affective symptoms and how they change over time in patients receiving IL-2 therapy, providers cannot know which symptoms to screen for, and the times at which screening should occur.

The lack of standardization in screening protocols may result in many symptoms being overlooked, under-reported and poorly managed. Although patients and families report sleep insufficiency as a primary concern, and researchers hypothesize that
cytokines are associated with sleep disturbance, studies measuring sleep quality in the IL-2 population were not found.

2.5 Conclusion

The etiology of cognitive and affective symptoms is unclear and may be difficult to explore because of the complicated clinical course of cancer patients. Capillary Leak Syndrome, which is a life-threatening side effect experienced by nearly all patients receiving intravenous IL-2, causes increased vascular permeability, leading to fluid shifting out of the circulatory system and into surrounding tissue, exacerbating other negative side effects of IL-2 (Mavroukakis et al., 2001), including cognitive and affective symptoms (Esper, 2012).

Another plausible etiology as seen in patients receiving chemotherapy is decreased and damaged white and grey matter; however, studies have not been conducted on brain matter in patients receiving immunotherapy (Monje & Dietrich, 2012). Alterations in brain matter may possibly lead to cognitive fatigue and cognitive/affective symptoms because IL-2 crosses the blood-brain barrier; however, some researchers lean more towards the theory that alterations in cognition and affect are related to fluid overload in the brain or cerebral edema, creating changes in brain functioning (Muehlbauer & White, 1998). Perhaps these alterations are more severe and acute in IL-2 patients than in chemotherapy patients.
Patients and family members have reported cognitive/affective symptoms to be the most alarming and difficult symptoms related to high dose IL2 treatment. For example, a family member described challenges of these side effects through her parent’s IL-2 experience:

The second one was brutal. [Parent] could take 8 doses but the mental side effects were more severe because her brain became very swollen. This time, she did not know where she was, who I was or what was going on. She could not fall asleep for 24 hours, hallucinating all the time that she was in a mental institution and that people were trying to take her place. Then, they gave her something for anxiety and she fell asleep, waking up only to go to the bathroom. Each time she woke up for the bathroom, she fought with me because she thought that the bathroom was not where I was leading her. (Bery, 2011)

Many patients agree that these symptoms are not adequately screened for and patients were not informed about these potential changes (Ejneary, 2011).

Our review of the literature confirms a lack of standardization when assessing, reporting and managing cognitive/affective symptoms. Longitudinal studies describing the trajectory of depression either ended with the completion of four cycles of IL-2 therapy (Musselman et al., 2013), or a month after IL-2 therapy finished (Capuron et al., 2002). We were unable to locate studies describing the trajectory of cognitive symptoms. To our knowledge, a study describing the degree of neurotoxicity in relation to the number of IL-2 cycles received by the patient has not been conducted. Although patients and family members describe sleep insufficiency as problematic, studies have not been conducted to quantify this loss of sleep in IL-2 patients.
While our understanding of patient side effects related to IL-2 administration has substantially improved, many important questions remain unanswered. Perhaps the largest uncertainty is the trajectory of IL-2—induced cognitive/affective symptoms. Patients and families describe cognitive/affective alterations as worrisome and debilitating, yet little emphasis has been placed on describing these symptoms. Furthermore, studies cannot be found that address whether patients return to baseline functioning after cessation of IL-2 therapy.

Although our review suggests altered cognition is present in high-dose IL-2 patients, the trajectories, breadth and depth of cognitive/affective symptoms have yet to be described. This is an essential step for the advancement of cognitive/affective symptom science in the IL-2 population. Despite intervention studies designed to address the psychosocial complications of IL-2, such as depression, mood swings, fear and tearfulness (Musselman et al., 2013), an understanding of the level of altered cognitive/affective symptoms experienced by IL-2 patients remains unclear. Without an in-depth, descriptive study elucidating the characteristics of the cognitive/affective symptoms experienced by IL-2 patients, family members and providers cannot know which symptoms to assess for in patients undergoing high-dose IL-2 therapy. Furthermore, we cannot alleviate these symptoms without an understanding of what the cognitive/affective symptoms are, the degree to which they are experienced, and how
these symptoms change over time with each consecutive cycle of IL-2 therapy. Future studies should focus on describing the trajectory of cognitive/affective symptoms in the high-dose IL-2 population. A mixed-method case study approach might be beneficial to describe the experiences of patients, informal caregivers and providers, and provide insight into these symptoms, when they appear, and how they change over time.

2.5.1 Implications for Practice

Nurses and family members are the first line of defense when assessing for acute changes in cognition and affect, and the importance of their roles should not be minimized. It is important to reassure patients and family members that alterations in cognition and affect are prevalent and expected, and efforts should focus on techniques such as relaxation and reorienting the patient when needed (Mavroukakis et al., 2001). Enlisting the help of social workers, and engaging family members in techniques to maintain patient safety during times of anxiety and confusion might also be beneficial (Mavroukakis et al., 2001). Cognitive/affective alterations in high-dose IL-2 is multifaceted, meaning that these alterations might be the result of any or all of these factors: fluid overload, IL-2 crossing the blood brain barrier, or the many concomitant medications used to reduce other severe side effects of IL2 treatment (Schwartz et al., 2002). In addition to keen assessment skills, nurses should also determine if there are
any pro re nata medications that might be contributing to or exacerbating these alterations, for example the use of Lorazepam to assist with sleep and anxiety.

High-dose IL-2 is shown to have a plasma distribution of 13 minutes, and a plasma half-life of 85 minutes following a 5-minute bolus infusion (Konrad et al., 1990), which might explain why most side effects are transient, peaking within 2- to 4-hours after the bolus IL-2 infusion.

Educating patients and family members on potential cognitive/affective alterations is essential. Nurses should institute the help of family members in assessing for acute cognitive/affective alterations, which might prove to reduce the anxiety of family members while improving outcomes for the patient. Finally, the trajectories, breadth and depth of cognitive/affective symptoms has yet to be described, which is an essential for the advancement of cognitive/affective symptom science in the IL-2 population.
3. Cognitive, Affective, and Sleep Symptom Experience During Cancer Treatment Using a Case Study Design

When previous cancer treatments have been unsuccessful, stage III and stage IV metastatic renal cell carcinoma (MRCC) patients are candidates for high-dose Interleukin-2 (IL-2), an immunotherapy used to heighten the body’s immune system to fight cancerous cells (American Cancer Society, 2010; National Cancer Institute, 2013b). This aggressive therapy offers patients a chance at remission but can result in iatrogenic cognitive, affective, and sleep disturbance symptoms (Fyfe et al., 1995; Mann, Dail, & Bailey, 2015). Unfortunately, these symptoms can cause patients or care providers to end treatment early, resulting in decreased treatment efficacy. Knowledge around the occurrence of symptom patterns, factors that impact symptom trajectory, and how individuals treated with this therapy experience these symptoms can be utilized to design interventions that allow individuals to manage symptoms and complete prescribed treatments, thus improving treatment efficacy.

Cognitive, affective, and sleep disturbance symptoms are among the most challenging symptoms for patients, care partners, and providers to manage, yet there is limited understanding of these symptom trajectories. Further, while standardized protocols exist to manage systemic changes such as cardiotoxicity and renal insufficiency, patients and nurses report that there is a lack of standardization in screening, reporting, and managing cognitive, affective, and sleep disturbance
symptoms (Mann et al., 2015). Importantly, cognitive (e.g., orientation, concentration, attention, memory) (McDonald, Flashman, Saykin, 2002; Vaughan, Agner, & Clinchot, 1997), affective (e.g., depression, anhedonia, aggression) (Mavroukakis et al., 2001; Muehlbauer & White, 1998; Myint et al., 2009), and sleep disturbance (e.g., insomnia, hypersomnia) symptoms are often interdependent and have synergistic effects. Investigating these symptoms in isolation, as is often done in pharmacotherapeutic research (Atkins et al., 1999; Fyfe et al., 1995; Rosenberg et al., 1994; White et al., 1994), may lead to an incomplete understanding of the totality of the individual’s experience. Examining the depth and breadth of symptoms and their interrelationships can lead to a deeper understanding of the IL-2 treatment experience, ultimately leading to improved interventions for patients and their care partner(s).

Renal cell carcinoma patients receiving high-dose IL-2, defined as 600,000-720,000 International Units/kilogram (IU/kg) of synthetic IL-2 administered intravenously over 15 minutes, receive up to 14 consecutive doses every eight hours as standard protocol. These 14 consecutive doses are administered in one of up to four treatment hospitalizations, also known as treatment cycles; one hospitalization can last up to five days (Atkins et al., 1999). Patients are discharged home for two weeks between treatment cycles and are readmitted to the hospital for as many of the four treatment cycles that the patient receiving IL-2 can tolerate. Rarely do patients receiving
IL-2 complete all 14 doses during one hospitalization because they experience severe systemic alterations (e.g., acute renal failure, cardiovascular toxicity, cognitive alterations) causing the patient or care provider to end treatment early. Because the majority of patients do not receive the 14 IL-2 doses during each hospitalization, it is important to determine differences in symptom trajectories between patients who do and do not complete the treatment due to dose-limiting toxicities. Researchers have reported a wide range of attrition rates in their IL-2 studies, where up to 50% of patients receiving IL-2 end treatment after cycle 1. An additional 25-50% of the remaining participants end treatment after cycle 2. Researchers report that by cycle 4, as few as 3% of all participants and at most one-third of the total participants receive cycle 4 of IL-2 therapy (Mann et al., 2015).

Because symptoms from IL-2 treatment can be cumulative, and can change with each dose and each hospitalization (J. P. Dutcher et al., 2014; Musselman et al., 2013), investigating cognitive, affective, and sleep disturbance symptoms within—and across—hospitalizations is important in understanding the dynamic trajectory of IL-2-induced symptoms, such as when symptoms arise, how they change over time, and their duration. Case study research methodology originated in the social sciences and has been used by scientists seeking to study complex, multifaceted research phenomena in their real-life contexts (Amerson, 2011; Anthony & Jack, 2009; Cronin, 2014; Crowe et al.,
2011), through the analysis of data collected from multiple perspectives and contexts (Amerson, 2011). Using a case study approach to investigate cognitive, affective, and sleep disturbance symptoms is important because many times patients treated with high-dose IL-2 therapy may be unaware of the changes that they are experiencing during treatment. Findings from a case study approach will allow patients receiving IL-2, their care partners, and their nurses set realistic shared expectations, and increase coping during and after treatment (Mann et al., 2015).

3.1 Objective

The purpose of this paper is to describe our evaluation of methods using a case study approach to collect quantitative and qualitative data from the patient, the care partner, and the primary nurse (PCPN) as a case triad to examine cognitive, affective, and sleep disturbance symptoms experienced by one patient diagnosed with MRCC receiving high-dose IL-2 (see Figure 4) during one hospitalization for treatment with IL-2. These findings served as the basis for implementing a larger scale study examining 10 IL-2 cases over a maximum of four treatment hospitalizations to explore the trajectory of symptoms experienced by the patient receiving IL-2.
3.2 Method

The Institutional Review Board (IRB) and the Cancer Protocol Committee of the participating hospital approved this study. The study team evaluated study procedures from the time of patient referral through the patient’s completion of treatment, appropriateness of measures completed by PCPN case informants to gain insight into the three symptom domains (cognitive, affective, and sleep disturbance), and the ability to yield data through a mixed methods case study approach to better understand the symptom experience of the patient receiving IL-2 during one hospitalization for treatment with IL-2.
Evaluation of the methods was an iterative process, occurring through weekly discussions as a study team (i.e. discussion about the referral, recruitment and enrollment procedures, acquiring buy-in from the unit manager, obtaining a waiver of consent to collect data from all nurses caring for the patient in addition to the consented and enrolled primary nurse, providing unit education to potential participating nurses, assessing the feasibility of the consenting, interviewing, measurement administration and transcription processes, and evaluating measurement tools to assess for alterations in the three symptom domains), observation of the PCPN case while in the inpatient setting (i.e. length of time and ease with which the measurement scales, semi-structured journal entries and recorded interviews were completed, feasibility of communicating with the nurse on the timing and schedule of treatment doses, and feasibility of the care partner to remain at the bedside during the treatment hospitalization), and post-treatment interviews with the case informants (i.e. assessing participant burden, and gathering recommendations for larger study).

3.2.1 Setting and Sample

Evaluation of study methods took place in 2015 at an inpatient oncology unit within a teaching hospital located in North Carolina and incorporated the perspectives of one MRCC patient receiving IL-2 therapy, his care partner, and his primary nurse. A waiver of consent was obtained from the IRB to collect de-identified data from nurses
who were not identified as the “primary nurse” caring for Andy (pseudonym). All other participants (PCPN case informants) provided written informed consent. The enrolled index participant, Andy, a white male in his mid-40’s, diagnosed with stage III MRCC, English-speaking and literate, was enrolled prior to hospital admission for his first dose of high-dose IL-2 therapy. Andy’s primary care partner was his wife, Maria (pseudonym), who planned to remain at Andy’s bedside during his hospitalization. The primary nurse, Allison (pseudonym), was a registered nurse who cared for Andy on three of the five days he was hospitalized for treatment. Allison was an experienced oncology nurse with more than a decade of experience administering high-dose IL-2.

Evaluation of methods occurred during weekly study team meetings initiated at the time the study was conceptualized through dissemination of the data.

### 3.2.2 Measures Completed by PCPN Case Informants

The study team evaluated the measures for feasibility (i.e. length of time to complete measures, ability to secure a private location to complete measures) and appropriateness (assessing if the selected measures were able to reflect the symptom changes experienced by the patient receiving IL-2 over the treatment course).

Quantitative and qualitative data were collected from three primary informants (PCPN triad). In addition to data collected from the primary nurse, a waiver of consent was
obtained to collect de-identified data from each nurse caring for the patient during his hospital stay.

Data included four questionnaires completed by the patient receiving IL-2 (the index participant), semi-structured journal entries completed by the care partner and nurses caring for the patient receiving IL-2, and a semi-structured interview completed by the patient receiving IL-2 and his primary nurse. See Table 5 for an overview of each measurement tool’s data informant, targeted symptom domain, and data collection time points.

**Table 5: Overview of the measures, their data informant(s), symptom(s) measured, and time points when each measure is to be completed**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Data Informant</th>
<th>Symptoms</th>
<th>Schedule of Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAM-A</td>
<td>Index Participant</td>
<td>Affective</td>
<td>Before dose #1 &amp; After last dose</td>
</tr>
<tr>
<td>IDS-C</td>
<td>Index Participant</td>
<td>Affective &amp; Sleep Disturbance</td>
<td>Before dose #1 &amp; After last dose</td>
</tr>
<tr>
<td>AFI</td>
<td>Index Participant</td>
<td>Cognitive</td>
<td>Before dose #1 &amp; After last dose</td>
</tr>
<tr>
<td>MoCA</td>
<td>Index Participant</td>
<td>Cognitive</td>
<td>Before dose #1 &amp; After last dose</td>
</tr>
<tr>
<td>Semi-Structured Journal Entry</td>
<td>Care Partner &amp; Nurse</td>
<td>Cognitive, Affective &amp; Sleep Disturbance</td>
<td>Before dose #1 &amp; Every 8 hours at the time of each IL-2 dose</td>
</tr>
<tr>
<td>Semi-Structured Interview</td>
<td>Index Participant and Primary Nurse</td>
<td>Cognitive, Affective &amp; Sleep Disturbance</td>
<td>After last dose</td>
</tr>
</tbody>
</table>

**3.2.2.1 Standardized Measures**

Measurement scales included the Hamilton Anxiety Scale (HAM-A) (Maier, Buller, Philipp, & Heuser, 1988), the Inventory of Depressive Symptomatology:
Clinician-Rated (IDS-C) (Rush et al., 2006; University of Pittsburgh, 2014), the Attentional Function Index (AFI) (Cimprich, Visovatti, & Ronis, 2011), and the Montreal Cognitive Assessment (MoCA) (Freitas, Simoes, Maroco, Alves, & Santana, 2012; Nasreddine et al., 2005; Rossetti, Lacritz, Cullum, & Weiner, 2011). See Table 6 for specific detail about each standardized measure, including psychometric properties.

Table 6: Standardized measures: psychometric properties

<table>
<thead>
<tr>
<th>Measure</th>
<th>Measurement Specifics</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAM-A</td>
<td>Investigator-administered</td>
</tr>
<tr>
<td></td>
<td>14 item questionnaire</td>
</tr>
<tr>
<td></td>
<td>Comprehensively measures anxiety symptoms</td>
</tr>
<tr>
<td></td>
<td>High internal consistency ($\alpha=0.77-0.92$) (Maier et al., 1988).</td>
</tr>
<tr>
<td>IDS-C</td>
<td>Investigator-administered questionnaire</td>
</tr>
<tr>
<td></td>
<td>30-item questionnaire</td>
</tr>
<tr>
<td></td>
<td>Comprehensively measures affective symptoms including sleep alterations (insomnias, hypersomnia) as IDS-C subscales</td>
</tr>
<tr>
<td></td>
<td>High internal consistency ($\alpha=0.96$) (University of Pittsburgh, 2014)</td>
</tr>
<tr>
<td></td>
<td>High inter-rater reliability ($\alpha=0.96$) (Baer, 2010)</td>
</tr>
<tr>
<td></td>
<td>Items related to weight gain on the scales (items 13 and 14) were omitted because nearly all patients receiving IL-2 gain weight related to Capillary Leak Syndrome, which is a side effect of the IL-2 treatment and not a sign of depression</td>
</tr>
<tr>
<td>AFI</td>
<td>Completed by the patient</td>
</tr>
<tr>
<td></td>
<td>13-item questionnaire</td>
</tr>
<tr>
<td></td>
<td>Measures concentration, mental fatigue, cognitive alterations, and confusion</td>
</tr>
<tr>
<td></td>
<td>High internal consistency ($\alpha=0.92$) (Cimprich et al., 2011)</td>
</tr>
<tr>
<td></td>
<td>For analysis, items (10 through 13) have been reverse-scored to reflect the same direction as the first nine items</td>
</tr>
<tr>
<td>MoCA</td>
<td>Investigator-administered</td>
</tr>
<tr>
<td></td>
<td>Measures global cognitive function (e.g., visuospatial abilities, orientation, executive functioning, abstraction, attention, language, short-term memory)</td>
</tr>
<tr>
<td></td>
<td>High internal consistency ($\alpha=0.90$) (Janice P. Dutcher et al., 2014; Freitas et al., 2012).</td>
</tr>
</tbody>
</table>
These four measures were specifically chosen to allow for the examination of three symptom constructs: cognitive, affect, and sleep disturbance. The HAM-A was selected to measure the trajectory of anxiety over the treatment course. The IDS-C, which includes a sleep subscale, was selected to measure depressive and sleep disturbance symptoms over the treatment course. The MoCA and the AFI measurement scales were selected to investigate the trajectory of cognitive symptoms over the treatment course.

A clinical neuropsychologist, with expertise in administrative and scoring procedures of these measures and how to distinguish between symptoms related to IL-2 side effects versus those related to changes in cognitive, affect, and/or sleep disturbance, trained the investigator. After collaborating, the study team decided to omit items related to weight gain (items 13 and 14 on the IDS-C) because nearly all patients receiving IL-2 gain weight related to Capillary Leak Syndrome, which is a side effect of the IL-2 treatment and not a sign of depression. The study team determined that it would be too burdensome for the patient receiving IL-2 to complete standardized measures every eight hours; therefore, the patient only completed these measures at pre- and post-treatment. The study team evaluated the standardized measures based on the time taken to complete these measures, and if the data yielded from these measurement tools aligned with the three symptom constructs (cognitive, affective, sleep disturbance).
3.2.2.2 Semi-Structured Journal

Instructions were given to the care partner and unit nurses, separately, on how to complete the semi-structured journal entries. These informants were asked to complete a journal entry every eight hours at the time a dose of IL-2 was administered to the patient. The care partner and the nurses were instructed to check the boxes of symptom change observed in the patient receiving IL-2 using a checklist of potential symptoms (e.g. altered language/speech, decreased concentration, mental fatigue, confusion, decreased attention/focus, decreased short-term memory, decreased orientation, increased depression, increased anxiety, mood alterations, sleep disturbances, hallucinations, increased sleep, decreased sleep, increased happiness, increased irritability) on the investigator-developed semi-structured journal. The instructions were also written and included at the top of each journal entry page.

This checklist was followed by two open-ended prompts asking the care partner (and nurse) to describe the symptoms observed in more detail. The first prompt asked, “For the boxes you checked above, please describe the changes you witnessed. When did the symptom appear? How long did the symptom last? How severe is the symptom? Can you describe the situation? Did anything make this symptom better or worse?” The second prompt read, “If there are other changes in the patient that you feel the team should know about, please feel free to write about these changes as well.”
The study team designed the semi-structured journal entry checklist and prompts with items informed by previous research findings including symptoms observed in the clinical setting and symptoms described on Internet-based patient forums (Ejneary, 2011; Mann et al., 2015). Because standardized measures were only administered to the patient receiving IL-2 at pre- and post-treatment, the team decided to time each journal entry for every eight hours to align with the administration of each IL-2 dose. The timing of this data collected from the care partner and nurses every eight hours provided insight into symptom trajectory change during and after each IL-2 dose.

The study team evaluated the feasibility of completing the semi-structured journal entries by asking the care partner and primary nurse about the time required to complete each entry, assessing the percentage of journal entries completed, and discussing if the checklist and open-ended follow-up questions provided unique, complementary data and insight into how the symptom trajectory changed with each subsequent dose of IL-2 treatment.

3.2.2.3 Semi-Structured Interviews

Semi-structured interviews were used to gather additional information surrounding symptoms acknowledged through care partner journal entries, nurse journal entries, and/or patient standardized measures. The semi-structured interviews with the patient and primary nurse contained open-ended questions designed to explore
and describe the cognitive, affective, and sleep disturbance symptom experience observed in the patient receiving IL-2. The purpose of the semi-structured interview was to elicit additional insights pertaining to symptoms observed or related to the patient receiving IL-2 over the course of all doses during the hospitalization. The study team created separate interview guides for the patient receiving IL-2 and his primary nurse (see Table 7).

Table 7: Example of semi-structured questions on the interview guide

<table>
<thead>
<tr>
<th>Category</th>
<th>Question(s)</th>
</tr>
</thead>
</table>
| Initial Open-Ended Questions | • Can you tell me about your relationship to Mr./Mrs._________?  
• Can you describe your level of familiarity with Interleukin-2 therapy [either as a nurse or as a patient]?  
• How many doses of IL-2 did he/she [you] receive?  
• Can you describe why treatment ended? |
| Intermediate Questions    | • Can you describe some of the cognitive, affective or sleep changes you experienced during your treatment?  
  ▪ When did this symptom first appear? How long did it last? How severe was this symptom? Explain the situation. Did anything make it better? Did anything make it worse?  
• Can you describe your role as the primary nurse? Can you describe the care partner role?  
• After reviewing the semi-structured journal entries that you completed over the past few days, I saw that your care partner mentioned that you experienced ________. Can you please describe the context, and situation?  
• Which alteration would you classify as most severe? Why? Which alteration would you classify as least severe? Why?  
• Are there any specific alterations you think we need to screen for more thoroughly?  
• [For the nurse.] Did the patient return to baseline before the next dose of IL-2, and if not can you explain the symptom pattern? |
| Ending Questions          | • Is there anything that you might not have thought about before that occurred to you during this interview? Is there anything you think I need to know? |
These semi-structured interviews were also used to gain additional insight into the methods used for evaluation purposes. For example, the patient receiving IL-2 was asked how long measurement scales took to complete and if this length of time was burdensome, and participants were asked for suggestions on how to improve the larger scale study. Interviews were evaluated by the time required for participation, ability to secure a private location to conduct the interview, willingness of informants to participate in the interview, ability to clearly hear the recorded interview when played back when the primary investigator transcribed the interview.

### 3.3 Data Collection Procedures

Prior to participant enrollment, the lead investigator met with the unit manager for the unit the study was taking place on to obtain buy-in, answer study related questions, address any concerns, and ask for guidance pertaining to gaining buy-in from unit nurses (i.e. scheduling an in-service to inform unit nurses of the upcoming study). The investigator conducted the in-service four times during one week: twice during the week (Monday through Friday) day shift, and twice during the week night shift. Because IL-2 treatment is always initiated on a Monday, and lasts a maximum of five-days, the study team determined it was not appropriate to provide in-services over the weekend day or night shifts. During the in-service, the lead investigator spent 10 minutes to explain the study. The investigator provided the unit nurses with handouts
that summarized the study, asked for input from the nurses about what they felt was important to include in the study and any suggestions, and answered questions.

The index participant for this case study, Andy, was identified and screened by the attending physician. The physician notified the study team by secure email that Andy was interested in participating in this study. The investigator then contacted Andy and his care partner, Maria, over the phone to briefly explain the study and to further assess their interest. Andy and Maria arrived at the oncology clinic prior to hospital admission for a preliminary workup. The investigator explained study roles, risks, and benefits to Andy and Maria separately in a private conference room in the clinic. Consent was then obtained from Andy and Maria separately prior to Andy’s admission to the hospital for IL-2 treatment. Upon Andy’s admission to the hospital unit, Allison, the primary nurse, verbally consented to a post-treatment interview and gave written consent prior to the interview.

After hospital admission, Andy completed one self-report (AFI) and three investigator-administered (HAM-A, IDS-C, MoCA) standardized measures prior to his first dose of IL-2 therapy and again after his last dose of IL-2. These scores served as Andy’s baseline and were compared to his post-treatment scores to determine which symptoms Andy experienced, the severity of the symptoms, and how these symptoms and their severity changed over the course of his treatment. Comparing baseline scores
to post-treatment scores provided a picture of the IL-2-induced cognitive, affective, and sleep disturbance symptom changes Andy experienced during his treatment hospitalization.

Maria, as well as each nurse caring for Andy, were asked to record their observations of Andy’s cognitive, affective, and sleep disturbance symptoms as a semi-structured journal entry prior to his first IL-2 dose and then after each IL-2 dose (every eight hours) for up to 14 doses during the hospitalization to provide data about the trajectory of Andy’s symptoms and how his symptoms changed for each IL-2 dose he received. Maria kept the journal in her possession throughout the hospitalization and gave it to the investigator prior to Andy’s discharge from the hospital.

Allison completed semi-structured journal entries for the days that she cared for Andy during the hospitalization, as well as an interview after Andy’s discharge. Allison was the nurse who cared for Andy for the most 12-hour shifts, and therefore knew Andy and his care best, which is why she was chosen as the primary nurse for this case. The investigator instructed Allison to assess and monitor Andy for cognitive, affective, and sleep disturbance symptoms throughout his hospitalization. The interview with Allison, which took place in a private room in the hospital after Andy completed all doses of his treatment, allowed the study team to gain additional data on cognitive, affective, and sleep disturbance symptoms she observed. This interview was recorded and transcribed.
In addition to data collected from these three case informants, the nurses who cared for Andy when Allison wasn’t working were asked to complete a semi-structured journal entry before the first dose of IL-2 was administered to Andy and then every eight hours at the time of each subsequent dose of IL-2. This semi-structured journal entry contained the same checklist and similar prompts to the entry completed by Maria. No identifiable information was collected from the unit nurses (with the exception of the consented primary nurse, Allison).

Nurses caring for Andy were contacted over the phone to determine the schedule of his last IL-2 dose, which was when he could no longer tolerate treatment. The investigator administered post-treatment measures in Andy’s private hospital room when treatment ended. Andy participated in a semi-structured interview, which was recorded and transcribed verbatim. This interview allowed the study team to understand the context (time and situation) in which the symptoms he reported in the measurement scales occurred. The goal of the interview was to understand when symptoms occurred, how long they lasted, the frequency, whether there were factors that initiated, exacerbated or alleviated these symptoms, and to assess the methods used in this study.
3.4 Results

Data collection procedures were feasible. The study team evaluated study procedures, which were primarily related to logistics. After conducting a broad evaluation of the study, the team analyzed the feasibility and processes, and the data yielded from the methods for each individual PCPN case informant.

3.4.1 Evaluation of Study Procedures

Notification from the provider of the potential participant was feasible. The provider communicated with the study team during the week prior to Andy’s treatment hospitalization notifying the team of the potential IL-2 patient. The provider notified the study team over email of Andy’s appointment date and time at the oncology clinic. Because eligibility for treatment with IL-2 is so specific, the study team believes referral through the provider is the most efficient way to recruit potential participants. For the larger scale study, the study team decided to email the provider each week to determine the patient schedule for the upcoming week to decrease the provider burden of notifying the study team of potential participants, and to be proactive about not missing potential participants. The provider was agreeable to this plan moving forward.

The study team decided to continue obtaining informed consent in a private room to maintain privacy and confidentiality of participants in the larger study. Similarly, the study team continued to consent the patient and care partner separately to
minimize the possibility of coercion by a case member. Written consent occurred prior to
the recorded interview with the primary nurse, and the primary nurse was willing and
excited to share her experience caring for the patient receiving IL-2.

The unit manager was essential in maintaining an open line of communication,
and fostering this relationship for future studies is necessary. The in-services provided
were an appropriate way to gain buy-in from unit nurses. Nurses felt invested in the
study when asked for input and several nurses stated they appreciated being notified of
the study prior to study initiation. Nurses asked questions about how to complete the
semi-structured journals, and questions surrounding the waiver of consent and the
collection of only anonymous data from nurses who were not identified as the
“primary” nurse. After having discussions with unit nurses, the study team determined
that these in-services are a necessary and important step to repeat prior to initiating
recruitment for the larger scale study.

After Andy was admitted to the hospital for treatment, the lead investigator
called the hospital unit daily to learn about the timing of Andy’s IL-2 doses (if Andy
received his dose or skipped his dose, if any). The lead investigator set up a password so
she was able to acquire patient information and updates over the phone. After calling
the hospital unit, the unit secretary transferred the lead investigator’s call to the nurse
caring for Andy for each shift. The nurse would give the investigator a quick update.
The primary nurse was asked in the follow-up interview if these calls were burdensome. Allison stated that the nurses on the unit are accustomed to regular phone calls from family members asking for patient updates and that this was not a burden nor did these calls add stress. Although these calls did not increase participant burden, the study team decided to gain approval to do a chart review of the electronic medical record to have access to nursing and provider notes, as well as have the ability to investigate the timing of each IL-2 and the patient’s medication history.

3.4.2 Patient-Specific Results: Feasibility/Process Results

Andy spent a total of 40 minutes at pre-treatment to complete the four investigator-administered and self-report measures and 50 minutes at post-treatment to complete the same measures with the addition of a semi-structured recorded interview. Pre-treatment measures were administered in a private room in the Cancer Clinic, while post-treatment measures were administered privately in Andy’s inpatient hospital room. The care partner was instructed to wait in the patient/family room on the unit while the lead investigator collected post-treatment measures. The first 40 minutes of the recorded interview was a recording of the standardized measures administered to the patient receiving IL-2 by the lead investigator. After the standardized measures were administered, the investigator asked the patient follow-up questions related to his
symptom experience over the treatment hospitalization. She also inquired about participant burden.

The study team decided to administer these four scales pre- and post-hospitalization (before the first dose of IL-2 and after the last dose of IL-2 when treatment ended) to minimize patient burden. Administering these measures every eight hours at the time of each IL-2 dose would have been very burdensome for the patient who was already very sick. Pre- and post-hospitalization measures allowed for the investigation of trajectory data while allowing the patient to focus on his treatment. The study team decided to keep these two time points for collection of the four standardized measures in the larger scale study. When asked about participant burden, Andy stated that the time required to complete the measures helped pass the time during while waiting in the cancer clinic. He also mentioned that while he did become increasingly fatigued as treatment continued, completing post-treatment standardized measures was possible; however, he also stated that he appreciated not having to complete 40 minutes of scales every eight hours at the time of each IL-2 dose.

The study team reviewed the transcription of the post-treatment interview with the patient receiving IL-2 and determined that recording the administration of the standardized measures was not beneficial. Instead, for the larger scale study, the recorded interview occurred after the standardized measures were completed. The lead
investigator would turn on the recording device, and then would ask follow-up
questions about timing, severity and duration of symptoms, as well as, unique symptom
experiences.

3.4.3 Patient-Specific Results: Data Yielded from Methods

Andy received eight of the maximum 14 IL-2 doses while inpatient for four days.
The four scales used to measure cognition, affect, and sleep disturbance identified
increases in these symptoms during the hospitalization. Scores on these scales (IDS-C,
HAM-A, MoCA, AFI) indicated that Andy experienced changes within each symptom
domain (cognition, affect, sleep disturbance) over the course of one IL-2 treatment
hospitalization (see Table 8), and these scales appropriately evaluated the three targeted
symptom domains. Increased scores on these standardized measures were confirmed by
qualitative reports of symptom change from the care partner on her semi-structured
journal entries.

Table 8: IL-2 patient’s measurement scores at pre-treatment (baseline) and post-
treatment time points

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Pre-Treatment Score</th>
<th>Post-Treatment Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDS-C</td>
<td>7</td>
<td>24</td>
</tr>
<tr>
<td>IDS-C Subscale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia (Items 1-3)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Hypersomnia (Item 4)</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>HAM-A</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>MoCA</td>
<td>24</td>
<td>17</td>
</tr>
<tr>
<td>AFI*</td>
<td>1195</td>
<td>560</td>
</tr>
</tbody>
</table>

*Items 10-13 are reversed. See text.
Andy went from experiencing a normal level of depressive symptoms at baseline to experiencing a moderate level at the post-treatment time point. While Andy reported mild initial insomnia (e.g. difficulty falling asleep) and moderate middle insomnia (e.g. difficulty staying asleep) at baseline, he reported sleeping between 14 to 16 hours during a 24-hour period by the end of treatment, indicating a state of hypersomnia as measured by the IDS-C.

Andy’s scores on the HAM-A also increased from pre- to post-treatment. While scores under 17 represent “mild” anxiety (Maier et al., 1988), this increase is concerning, particularly if symptom levels (e.g. anxiety, depressive symptoms) do not return to baseline before his next hospital admission for IL-2 therapy.

Andy’s scores on the MoCA decreased over one hospitalization, indicating moderate cognitive impairment at the post-treatment time point. Andy’s scores on the MoCA were in alignment with Maria’s reports. Both indicated that his cognitive symptoms worsened as IL-2 treatment progressed, particularly with tasks such as abstraction, verbal fluency, basic subtraction, and attention.

Andy’s scores on the AFI decreased from 100 (“extremely well”) at pre-treatment to 20 (“not at all”) at post-treatment on the following items: getting started on tasks (i.e. returning missed phone calls while in the hospital), following through with plans, doing things that take time and effort, and remembering to do the things you started. His
scores decreased from a 100 at pre-treatment to a 0 at post-treatment on the following items: making your mind up about things, keeping your mind on what you are doing, and keeping your mind on what others are saying. Andy reported no changes in forgetting to do important things, being patient with others, or keeping self from saying or doing things you did not want to say or do. Andy experienced severe alterations in attention over his treatment hospitalization; self-reported scores on the AFI are consistent with clinician-rated scores on the attention subscale of the MoCA, indicating severe alterations in attention. Additionally, in the post-treatment interview, Andy explained in response to fatigue, “I have had no energy to do nothing. I have just been out of it. I have no memory now. I couldn’t tell you right now why they even said they were quitting this treatment. I was doing good until today. It’s been bad, terrible.”

3.4.4 Care-Partner-Specific Results: Feasibility/Process Results and Data Yielded from Methods

The semi-structured journal entries completed by the care partner every eight hours at the time a dose of IL-2 was administered to the patient was beneficial in collecting symptom trajectory data during the treatment hospitalization when the patient was exhausted and unable to engage. Maria was asked about participant burden when she submitted her journal to the study team. When asked for the length of time required to complete each journal entry, Maria stated the entries were not burdensome and required roughly 5 minutes to complete. Maria successfully completed 100% of the
required journal entries, which was nine journal entries for this treatment hospitalization, one baseline entry followed by an entry for each dose of IL-2. Maria used both the check boxes, and the extra space provided following the semi-structured follow-up questions to elaborate on the symptoms she endorsed on the checklist. The study team determined that the investigator-developed semi-structured journal checklist and open-ended prompts were appropriate in gathering symptom trajectory data. Maria was able to identify acute symptom changes because of how well she knew her spouse. Maria vocalized her comfort with journaling and reported that journaling reduced her anxiety and stress. Maria also mentioned that journaling had become a routine for her since Andy’s cancer diagnosis. She said journaling allowed her to keep track of Andy’s symptoms, treatment changes, and questions for Andy’s doctors.

The lead investigator collected field notes, documenting feedback provided by Maria; however, the care partner was not included in the recorded post-treatment interview. The study team decided that the care partner provided such rich data which the team would have liked to follow up on through a recorded interview. For this reason, all case informants participated in a recorded post-treatment interview in the larger study. These face-to-face recorded reports of the treatment symptom experience were invaluable, as it helped the team to understand the challenges the patient faced during treatment, gave the team the opportunity to ask follow-up questions to gather
additional information, and cleared up ambiguities surrounding why treatment ended and what happened in other specific situations. For this reason, in the larger-scale study, each PCPN case informant was interviewed, including the care partner.

As part of the inclusion criteria, the study team required the care partner to stay at the patient’s bedside for the duration of the inpatient hospital stay. This was required because the study team believed that the care partner staying at the bedside during treatment was necessary for identifying symptom changes in their loved one. Andy’s care partner agreed to remain at her husband’s bedside during his hospitalization; however, Maria ended up leaving the hospital for an emergency and was unable to make it back to the hospital for two days. Although she was away from the hospital for 48 hours, she routinely called her husband to gauge how he was handling treatment. She also called the hospital unit to speak with his nurse for each shift to get updates pertaining to Andy’s treatment and symptom experience. Over the phone, Maria was still able to gather valuable information from her husband. For example, she was able to detect changes in his short-term memory and speech. Despite Maria’s distance from her husband during this time, she was diligent in following up with Andy over the phone and successfully completed her nine journal entries. Importantly, because of her familiarity with Andy, Maria was able to identify changes in symptoms nurses could not identify. For example, Maria checked boxes indicating that Andy experienced altered
speech, decreased concentration, mental fatigue, confusion, decreased short-term memory, and increased anxiety. She wrote in her corresponding journal entry: “[Andy] seemed very confused. He kept repeating himself. Very slurred, slow speech. He just seemed weak...” For the larger scale study, the research team decided to allow for the inclusion of care partners who may have to leave the bedside intermittently during the hospital stay, provided they agree to be active participants, checking in with the patient and nurse routinely.

3.4.5 Primary-Nurse-Specific Results: Feasibility/Process Results and Data Yielded from Methods

The post-treatment interview with the primary nurse took 30 minutes to complete. Similar to Andy, Allison was asked about participant burden in her semi-structured recorded interview. Allison reported that the time required to complete the semi-structured journal was minimal; however, she suggested that in the future the primary nurse should be allowed to participate in the interview over the phone. The unit manager requested for the 30-minute recorded interview to not occur during the 12 hours when the nurse was on the clock; therefore, this interview either had to occur before the shift, after the shift, or on a separate return to the hospital when the nurse was off duty. Because this makes for such a long day, the study team agreed that for the larger study, consent occurred in person, but it interviews could be completed over the phone.
Allison stated that Maria was invaluable in detecting changes in cognitive, affective, and sleep disturbance symptoms. Allison verbalized that greater emphasis should be placed on managing these symptoms in patients receiving IL-2. While symptoms such as changes in renal function and cardiotoxicity are managed, cognitive, affective, and sleep disturbance symptoms are neglected. Perhaps training is needed to educate nurses on how to identify and manage these symptoms to improve the patient symptom experience during the course of their treatment.

After the study team reviewed Maria’s journal, the investigator asked Allison follow-up questions to gather additional details surrounding the symptoms Maria observed in Andy. Allison was asked to explain any alterations in short-term memory and/or mental state that she observed in Andy. Allison responded,

And that one is harder for me as his nurse to know because I don’t typically ask the patient to remember things that I have told him. So that’s entirely possible. And those are not things that I would necessarily be able to pick up on because I am not expecting him to recall something for me...And because these patients are only hospitalized for five days, we aren’t telling them you must get up...We are just telling them, you may lay in the bed. It is just fine. We almost don’t worry about what is their mental state as much. So we don’t really pay as much attention to it.

3.4.6 Key Features of Case Triad

This PCPN case study highlighted the importance of including the patient receiving IL-2 in the IL-2 case, along with their care partner and primary nurse. Each member of the case was able to contribute unique data that offered insight into the
patient symptom experience, which when integrated, provided a comprehensive picture of the symptoms and the time points at which each symptom occurred. While the primary nurse provided clinical expertise, the care partner was able to add depth to the evaluation of her husband, specifically in regard to when his behavior deviated from baseline. This is particularly important in circumstances when medical professionals do not systematically assess cognitive, affective, and sleep disturbance symptoms, and therefore, these symptoms are often overlooked and neglected.

Andy experienced symptoms in each symptom domain (cognitive, affective, sleep disturbance) across treatment duration. The data from this case study illuminated the severe symptom alterations that Andy experienced during and after IL-2 treatment. Analysis of this case study highlighted the importance of following the IL-2 case over the treatment trajectory (within—and across—all hospitalizations), because patients can become symptomatic of alterations in cognition, affect, and sleep disturbance as early as after completing their first dose of IL-2. Furthermore, patients may be unaware of these alterations or may have memory lapses in what actually occurred during and after treatment.

3.5 Discussion

Using a PCPN case triad is feasible and provided the study team with rich, varied data that gave a picture of the patient symptom trajectory over the course of one
treatment. Patient scores on quantitative standardized measures were enhanced by qualitative symptoms witnessed by the care partner and nurse, described through semi-structured journal entries and recorded interviews. Although many research questions can be answered with quantitative or qualitative methods alone, a comprehensive understanding of the problem is lacking (Douglas, 2003). Although vastly different, these methodologies can be thought of as complementary (Curry, Nembhard, & Bradley, 2009), filling in gaps, allowing the full picture to emerge from the data. This case study highlights how the methods used can be a unique and rich mechanism used to collect quantitative and qualitative data from multiple case informants to give a comprehensive picture of treatment and symptom trajectories in a wide array of patient populations with chronic illnesses.

This study provided evidence of the rich and unique data that can be collected using a mixed-method case study approach, which the study team used in its larger-scale study that explored 10 IL-2 cases over all treatment doses (up to 14 per hospitalization) and over all treatment hospitalizations (up to four). A case study design allowed investigators to trial measures and explore the wide range of symptom trajectories experienced by each unique case, while allowing for data saturation and triangulation. This case study methodology can be applied to other chronic illness populations where patients undergo aggressive treatment over multiple time points to
help researchers and clinicians better understand their patient’s symptom trajectory and treatment experience, and therefore, design tailored interventions to target unique challenges within each individual case.
4. Trajectory of Cognitive Symptoms in Patients Receiving High-Dose Interleukin-2 Therapy

4.1 Background

An estimated 64,000 people were diagnosed with kidney and renal pelvis cancer in 2017 (National Cancer Institute, 2017). Roughly 68% of individuals diagnosed were male, and the average age at diagnosis was 64 years (American Cancer Society, 2017b). Renal cell carcinoma is the most common type of kidney cancer and is comprised of two subtypes based on cellular presentation as observed under a microscope. These subtypes include clear cell and papillary carcinoma, which comprises approximately 92% and 8% of the renal cell carcinoma population, respectively (The Cancer Genome Atlas, 2017).

Treatment for renal cell carcinoma is dictated by the progression of the cancer (i.e. stage of the cancer). Individuals diagnosed with stage II, III, or IV clear cell renal cell carcinoma undergo a partial or radical nephrectomy prior to initiation of follow-up/surveillance (National Comprehensive Cancer Network, 2017). For stage IV renal cell carcinoma with a clear cell histology or relapsed stage II or III carcinoma after surgical removal of the cancer, there are a number of available first-line chemotherapies and immunotherapies for patients based on their performance status and organ function prior to therapy induction (National Comprehensive Cancer Network, 2017). High-dose Interleukin-2, hereafter referred to as IL-2, is one of the first-line therapies
available for individuals with a clear cell histology who are otherwise healthy (i.e. have good performance status, good organ function, and minimal co-morbidities) individuals living with cancer (National Comprehensive Cancer Network, 2017).

The main goal of IL-2 therapy is to heighten the body’s immune system by stimulating T-cell growth (American Cancer Society, 2017a; National Institutes of Health, 2018). This initiated immune response helps the patient fight cancer, decreasing the spread of the disease with the aim of placing the patient in remission. While only a small subset of patients diagnosed with renal cell carcinoma responds to treatment with IL-2, this immunotherapy is the only treatment that has produced durable, lasting results (American Cancer Society, 2017a). Unfortunately, severe cognitive symptoms may result in early termination of IL-2 therapy, which would prevent the patient from achieving remission.

Altered cognition includes inefficiencies or impairments in concentration, attention, short-term memory, executive functioning, abstraction, language, basic arithmetic, and orientation (McDonald et al., 2002; The American Psychiatric Textbook of Neuropsychiatry, 1999; Vaughan et al., 1997). While some cognitive symptoms are transient, lasting a short duration during treatment (e.g. confusion), other symptoms may have residual effects, persisting even after the end of treatment (e.g. attention, fatigue) (Musselman et al., 2013). In some patients, these symptoms continue
throughout the remainder of their life (Myint et al., 2009). Researchers have found that up to 75% of cancer patients receiving treatment experience alterations in cognition, and patients report that these alterations severely impact their quality of life (e.g. work life, home life, relationships) (Von Ah, 2015). Furthermore, 35% of cancer patients report changes in cognition persisting months and years after treatment has ended (Janelsins, Kesler, Ahles, & Morrow, 2014). To date, the majority of research investigating cognitive alterations has occurred in the breast cancer population in patients receiving chemotherapy (Janelsins et al., 2014). Unfortunately, patients receiving immunotherapy also experience altered cognition. Because these alterations can have lasting effects, it is important for researchers to study the cognitive symptom trajectory during and after treatment to better understand what symptoms occur and how they change over time.

Studying the trajectory of IL-2-induced cognitive symptoms that patients receiving IL-2 for renal cell carcinoma experience within and across hospitalizations using a case study approach can help clinicians and researchers better understand how these symptoms change over time and follow unique patterns and characteristics within individuals (J. P. Dutcher et al., 2014). High dose IL-2 is defined as 600,000-720,000 international units/kilogram of synthetic IL-2 administered intravenously as a 15 minutes bolus, every eight hours for up to 14 consecutive doses; each set of 14
consecutive doses constitutes one of up to four treatment cycles for IL-2 therapy (Atkins et al., 1999). The dosing regimen of IL-2 is such that patients often experience cumulative effects that worsen as treatment continues, which is why it is important to study these cognitive symptoms within- and across- each hospitalization for IL-2 therapy. Understanding the dynamic trajectory of these symptoms, such as when they arise, patterns in how they cluster and change over time, and their duration is an important first step to understanding the breadth of these cognitive symptoms and is critical to then design and test targeted interventions to alleviate treatment-limiting symptoms.

Therefore, the purpose of this report is to describe the trajectory of cognitive symptoms experienced by patients receiving IL-2 for renal cell carcinoma, within and across hospitalizations. Data were collected from the patient receiving IL-2, their care partner, and their primary nurse using a mixed-methods case study approach. A total of ten IL-2 cases were followed for up to four hospitalizations for IL-2 therapy. The research team then chose three case exemplars with unique characteristics and attributes that best described the trajectory of cognitive symptoms to highlight key patterns in symptoms observed in or reported by patients. The specific aims of this study were to:
• Aim 1: Describe transient and residual cognitive (language, concentration, confusion, attention, short-term memory, and orientation) symptoms in patients receiving IL-2 during up to four hospitalizations for IL-2 therapy.

Aim 2: Describe transient and residual cognitive symptoms as qualitatively reported by each patient’s care partner and primary nurse during each hospital admission for IL-2 therapy.

Aim 3: Describe the trajectory of transient and residual cognitive symptoms in patients receiving IL-2 over the total number of hospitalizations, synthesizing patient data with care partners, and nurse reports of symptom change.

4.2 Methods

4.2.1 Design

The study team used a descriptive, exploratory, mixed-method case study approach to describe the longitudinal trajectory of cognitive symptoms expressed in MRCC patients receiving IL-2 through qualitative and quantitative analyses of each case. Each case was comprised of the patient receiving IL-2, their care partner, and their primary nurse, which gave researchers access to rich data from three case informants across each hospitalization (up to four hospitalizations) for as many as 14 doses (five days of therapy).
4.2.2 Setting

MRCC patients undergoing IL-2 treatment and their care partners were recruited for this study in a cancer clinic at a teaching hospital located in North Carolina prior to their hospital admission. For each hospitalization, patients receiving IL-2 (and their care partners) stayed on a 24-bed cancer unit at the teaching hospital where patients could be frequently monitored. The primary nurse gave verbal consent at the time of the patient’s admission and provided written consent prior to his or her interview. Rotating clinic providers in the hospital manage the treatment of patients receiving IL-2. The Institutional Review Board and Cancer Protocol Committee granted approval for the study to be conducted at the teaching hospital.

4.2.3 Sample

Each patient receiving IL-2 (index participant) enrolled in the study was diagnosed with stage III or IV MRCC, was between the ages of 18 to 65 years, could read and write in the English language, and received IL-2 therapy that followed standard IL-2 dosing protocol at the teaching hospital. The patients in this study were limited to patients diagnosed with stage III and IV disease because only patients with progressed disease are eligible for high-dose IL-2 therapy. Participants had a score of 0 or 1 on the Eastern Cooperative Oncology Group Performance Status, per the teaching hospital’s IL-2 administration guidelines, and national practice guidelines for IL-2
administration, as a lower score on this measure is associated with better treatment response rates (J. P. Dutcher et al., 2014). Patients involved in this study also had to have a primary care partner (family member or friend) present with them and/or active in their care during IL-2 therapy.

Exclusion criteria included a previously documented cognitive disorder (e.g. dementia), metastases to the brain, congenital brain defects, or traumatic brain injury, as it would have been difficult to determine if cognitive symptoms in such patients were related to IL-2 therapy.

The care partner was defined as the primary family member or friend who stayed with the patient at the hospital during the patient’s IL-2 therapy, or agreed to serve as an active participant in the patient’s care (i.e. calling the unit nurses for updates if he/she had to leave the hospital, calling the patient room to check-in). Care partners were 18 years of age or older because of the level of maturity required to journal about the patient’s treatment, and to witness and report alterations during the patient’s treatment.

The primary nurse in this study was identified by the unit manager or self-identified as the nurse who best “knows” the patient receiving IL-2 and his or her care. The primary nurse was always a registered nurse. While care partners remained the same for each hospitalization, primary nurses changed, which increased the depth of
the data for each case.

The nurses other than the primary care nurse who cared for the patient receiving IL-2 were not included in the “IL-2 case” but contributed de-identified data when the primary nurse was not scheduled to work. A waiver of consent was granted through the Institutional Review Board to collect de-identified data from unit nurses. As part of their hospital unit training, nurses were trained on how to care for patients receiving IL-2. These experienced oncology nurses receive additional training on IL-2 administration and the associated patient care before they can be assigned to care for a patient receiving IL-2. These nurses follow an IL-2 treatment protocol and are in constant consultation with the overseeing provider.

**4.2.4 Instruments and Measures, and Data Collection Time Points**

**4.2.4.1 Standardized Measures**

Cognitive symptom alterations in the patient receiving IL-2 were measured with two standardized measurement scales at two time points for each hospitalization: before the first IL-2 dose (pre-treatment) and immediately after the last dose (post-treatment) of IL-2. Standardized measures included the Attentional Function Index (AFI) (Cimprich et al., 2011), and the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). See Table 9 for an overview of the measurement tools, who completed the tools, and the data collection time points.
Practice Effects. Because of the high probability that participants might score better on the MoCA after being administered the scale several times, three MoCA versions (7.1, 7.2, 7.3) were used to minimize artificial inflation of scores through practice effects (Netley, Rachman, & Turner, 1965). The MoCA versions were randomized to the patient’s hospital admission number (1, 2, 3, 4) so that the patient receiving IL-2 received a different version of the MoCA for the first three hospital admissions, and then the same version for admissions 1 and 4. The same MoCA version was used for the pre- and post-treatment assessments within each hospitalization.
### Table 9: Cognitive assessment measurement tools

<table>
<thead>
<tr>
<th>Measure</th>
<th>Details, Variables, Psychometric Properties, and Data Collection Time Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic Data</strong>&lt;br&gt;Questionnaire; Electronic Medical Record</td>
<td>• Race, gender, age, marital status, cancer staging, and treatments prior to IL-2 therapy&lt;br&gt;• Collected through an enrollment questionnaire&lt;br&gt;• Collected through a chart review of the electronic medical record</td>
</tr>
<tr>
<td><strong>Quantitative</strong>—Completed by the Patient receiving IL-2 at Pre- and Post-treatment</td>
<td>• 13-item questionnaire completed by the patient&lt;br&gt;• Measures concentration, mental fatigue, cognitive alterations, and confusion&lt;br&gt;• For analysis, items (10 through 13) were reverse-scored to reflect the same direction as the first nine items&lt;br&gt;• Scoring:&lt;br&gt;  o The index participant was asked to rate themselves on a 100-point sliding scale for each item ranging from 0 = “not at all” to 100 = “extremely well” increasing in 5 point increments; the direction of the scale is opposite for items 10 - 13&lt;br&gt;  o Score of 1300 = no changes in self-reported attention; Scores close to 0 = very severe alterations in attention</td>
</tr>
<tr>
<td><strong>AFI Attentional Function Index</strong></td>
<td>• Investigator-administered&lt;br&gt;• Measures global cognitive function (e.g., visuospatial abilities, orientation, executive functioning, abstraction, attention, language, short-term memory)&lt;br&gt;• Total scores range from 0 to 30:&lt;br&gt;  o Scores &gt;/= 26: intact global cognitive functioning&lt;br&gt;  o Scores 18-26 = “mild” cognitive impairment; Scores 10-17 = “moderate” impairment; Scores &lt; 10 = “severe” impairment (Nasreddine et al., 2005).&lt;br&gt;• High internal consistency (α=0.90) (Janice P. Dutcher et al., 2014; Freitas et al., 2012).</td>
</tr>
<tr>
<td><strong>MoCA Montreal Cognitive Assessment</strong></td>
<td>• Investigator-developed semi-structured journal entry containing a checklist of symptoms observed in the patient receiving IL-2, followed by an open-ended prompt asking for expansion on symptoms witnessed in the patient receiving IL-2.</td>
</tr>
<tr>
<td><strong>Qualitative Journal Entry—Completed by Care Partner and Nurse(s) at Pre-treatment and time of each IL-2 dose</strong></td>
<td>• In depth, recorded, semi-structured interview used to explore and describe the trajectory of transient and residual IL-2—induced cognitive symptoms witnessed in or experienced by the patient receiving IL-2.</td>
</tr>
</tbody>
</table>
**Study Burden.** To minimize the time required to complete standardized measures by patients receiving IL-2, these measures were completed twice (pre- and post-treatment) during each hospitalization rather than every eight hours. Together, these two standardized measures provided insight into IL-2-induced cognitive symptoms in MRCC patients receiving IL-2. Pre-treatment scores on these standardized measures completed at the time of each hospital admission were used as a baseline and compared to post-IL-2 treatment scores to assess which symptoms the patient receiving IL-2 experienced, the severity of the symptoms, and how these cognitive symptoms and their severity changed over the course of treatment for the index participant.

**4.2.4.2 Semi-Structured Journal**

The care partner, primary nurse, and unit nurses (when the primary nurse was not working) each individually completed the semi-structured journal entries. These informants were asked to complete a journal entry every eight hours at the time a dose of IL-2 was administered to the patient. The care partner, primary nurse, and unit nurses were instructed to check the boxes of symptom changes, if any, observed in the patient receiving IL-2 using a checklist of potential cognitive symptoms (e.g. altered language/speech, decreased concentration, mental fatigue, confusion, decreased attention/focus, decreased short-term memory, decreased orientation) on the
an investigator-developed semi-structured journal. These instructions were also written and included at the top of each journal entry page.

This checklist was followed by two open-ended prompts asking these case informants to describe the symptoms observed in more detail. (See Appendix for open-ended journal entry prompts. See Chapter 3 for rationale surrounding data collection time points.)

4.2.4.3 Semi-Structured Interview

Each case informant individually participated in a recorded, post-treatment semi-structured interview with the lead investigator at the end of each treatment hospitalization after the last dose of IL-2 was administered. These semi-structured interviews were used to gather additional information surrounding symptoms acknowledged through care partner journal entries, nurse journal entries, and/or patient standardized measures. The semi-structured interviews with the patients receiving IL-2, care partners, and primary nurses contained open-ended questions designed to explore and describe the cognitive symptom experience observed in or by the patient receiving IL-2. The study team created separate interview guides for the patients receiving IL-2, care partners, and primary nurses. (See Appendix for semi-structured interview guides.)

Figure 5 is a model illustrating the longitudinal data collected from each case informant over each treatment hospitalization using a case study approach to
understand the trajectory of cognitive symptoms experienced by or observed in the patient receiving IL-2. Not all patients were admitted four times for IL-2 therapy. Per IL-2 standard protocol, a computed tomography (CT) scan was used to evaluate if patients receiving IL-2 responded to IL-2 therapy after two treatment cycles. If the patient showed no disease improvement, or disease stability, the patient would cease IL-2 treatment and discuss alternative treatments with the provider. Continuation of treatment with IL-2 depended on a) disease progression and b) side effect toxicity. Therefore, the symptom trajectory was described for the treatments completed in situations where patients did not complete the maximum four hospitalizations.
4.3 Procedures

4.3.1 Recruiting and Consent

Ten patients receiving IL-2 with a MRCC diagnosis were enrolled using purposeful convenience sampling (Teddlie & Yu, 2007). A provider in the cancer clinic who was examining patients notified the study team of potential participants through secure email the week prior to their arrival. The lead investigator met with potential participants in a private clinic room. She explained study roles, risks, and benefits to
potential participants (patient and care partner) separately in a private conference room in the clinic. If patients agreed to participate, consent was obtained separately prior to admission to the hospital for IL-2 treatment.

Upon the patient’s admission to the hospital unit, the primary nurse verbally consented to an in-person or over-the-phone recorded post-treatment interview and gave written consent prior to the interview. While the primary nurse for each participant and hospitalization changed, the care partner for each patient receiving IL-2 remained consistent across the patient’s treatment hospitalizations. In circumstances where the primary nurse remained the same, or where the unit nurse served as the primary nurse for another patient receiving IL-2, he/she was re-consented for each interview. A waiver of consent was obtained from the IRB to collect de-identified data from nurses who were not identified as the “primary nurse” but cared for the patient receiving IL-2.

4.3.2 Data Collection Procedures

After hospital admission, the patient scheduled to receive IL-2 completed two standardized measures evaluating baseline cognitive symptoms: one self-report (AFI) and one investigator-administered (MoCA) measure. These measures were repeated again after the last dose of IL-2, and this pattern of data collection was repeated for each subsequent treatment hospitalizations that the patient completed.
The care partner was instructed to record his or her observations of the index participant’s cognitive symptoms as a semi-structured journal entry prior to the first IL-2 dose and then after each IL-2 dose (every eight hours) for up to 14 doses during each hospitalization to provide data about the cognitive symptom trajectory, and how cognitive symptoms changed with each dose of IL-2 and each hospitalization for treatment. Care partners returned journal entries to the lead investigator during their recorded semi-structured post-treatment interview.

Primary nurses completed semi-structured journal entries for the days they cared for the index participant during the hospitalization, as well as a recorded semi-structured post-treatment interview prior to the index participant’s discharge. The lead investigator instructed the primary nurse to assess and monitor the patient receiving IL-2 for cognitive symptoms throughout the hospitalization. The interview with the primary nurse occurred either in a private room in the hospital or over the phone. Consent of the primary nurse was always given in person prior to the interview over the phone. This interview was recorded and transcribed.

In addition to data collected from these three case informants, nurses who cared for the index participant when the primary nurse was not working were asked to complete a semi-structured journal entry before the first dose of IL-2 was administered to the patient receiving IL-2 and then every eight hours at the time of each subsequent
dose of IL-2. This semi-structured journal entry contained the same checklist and similar prompts to the entry completed by the care partner. No identifiable information was collected from the unit nurses (with the exception of the consented primary nurse).

A chart review of the electronic medical record was used to collect demographic data and to follow the treatment schedule of the patient receiving IL-2. Nurses caring for the index participant were contacted over the phone to confirm when the last IL-2 dose was administered, which was when the patient receiving IL-2 could no longer tolerate treatment. When treatment ended, the investigator administered post-treatment standardized measures in the index participant’s private hospital room and conducted and recorded a semi-structured interview, which was recorded and transcribed verbatim. This interview allowed the study team to understand the context (time and situation) in which the symptoms reported in the standardized measures occurred. The goal of the interview was to understand when symptoms occurred, the frequency and duration of these symptoms, and whether there were factors that initiated, exacerbated, or alleviated the reported symptoms.

Prior to discharge, the lead investigator confirmed the upcoming treatment schedule with the patient receiving IL-2 and their care partner. For example, after cycle 1, the investigator confirmed the start date for cycle 2. After cycle 2, the investigator confirmed when the index participant was scheduled for the cycle 2 post-treatment
follow-up scan. Results from the follow-up scan dictated whether the index participant was finished with IL-2 treatment (i.e. no longer eligible to receive treatment because he/she did not show disease improvement), or if the patient receiving IL-2 would be admitted for two additional treatment cycles (cycle 3 and cycle 4). The data collection procedure described above was replicated for each subsequent treatment cycle/hospitalization for which the index participant was enrolled.

### 4.4 Data Analysis

Data preparation occurred prior to data analysis. Scores for each individual item on the standardized cognitive measures (AFI, MoCA) were entered into an Excel spreadsheet. A professional transcriptionist was hired to transcribe all qualitative data into text stored in a Microsoft Office Word document. These textual data included journal entries from the care partner; recorded interviews with the patient receiving IL-2, the care partner, and the primary nurse; and field notes. The study team verified the accuracy of all transcribed documents by randomly selecting 10% of the transcribed documents and reviewing them for validity and consistency of information (Campbell, Quincy, Osserman, & Pedersen, 2013).

The research team conducted case study data analyses concurrently with data collection beginning after the first hospitalization of the first IL-2 case. Researchers first analyzed each case as a standalone unit (detailed in the following section). After
thoroughly analyzing each case, the research team selected three cases as exemplars of IL-2-induced cognitive symptoms. The overall aim was to examine the trajectory of cognitive symptoms each patient receiving IL-2 experienced using data from each case informant. Case study analysis involved organizing and examining all data pertaining to the case. Data for each case consisted of quantitative and qualitative data gathered from each case informant (patient receiving IL-2, care partner, primary nurse) and nurses from up to four hospitalizations. Each hospitalization included data from up to 14 IL-2 doses, and contained data including scores on standardized measures completed by the index participant, care partner and nurse journal entries from each IL-2 dose, and interviews with the index participant, care partner, and primary nurse. The across-case comparisons involved comparing cases to identify commonalities and differences to direct future research (Khan & VanWynsberghe, 2008).

### 4.4.1 Within-Case Analysis

Analysis of each case began with a description of demographic variables (See Table 11).

**Aim 1:** Describe transient and residual cognitive (language, concentration, confusion, attention, short-term memory, and orientation) symptoms in patients receiving IL-2 during up to four hospitalizations for IL-2 therapy. For quantitative data analysis of the total study sample, total scores from the two standardized measures
(MoCA, AFI) administered to the patient receiving IL-2 were scored at pre- and post-treatment time points for each hospitalization to assess alterations in cognition. The mean total scores for the two standardized measures (MoCA, AFI) for the ten patients receiving IL-2 were mapped on a graph at pre- and post-treatment for each cycle for visual inspection to understand the study sample as whole, and to visually analyze the cognitive symptom trajectory (Onwuegbuzie & Dickinson, 2008). For quantitative data analysis of each individual case, after graphing mean scores for the study sample, the total score for each patient receiving IL-2 were individually graphed using the same technique described above. Pre-treatment total scores on the standardized measures for each hospitalization were compared across all hospitalizations to further assess long-term symptoms in each patient receiving IL-2. For example, pre-treatment total scores on the AFI (measuring “attention”) for hospitalizations 1, 2, 3, and 4 were compared to determine if the patient returned to his/her baseline attention level prior to the next treatment hospitalization. For qualitative data analysis, patient interviews for each case were analyzed using content analysis (Hsieh & Shannon, 2005) supported by the use of ATLAS.ti ("ATLAS.ti: Qualitative Software," 2014; Silver & Lewins, 2009). See Table 10 for detail about qualitative data analyses.
Table 10: Qualitative data analysis using content analysis

<table>
<thead>
<tr>
<th>Coding Level</th>
<th>Process</th>
</tr>
</thead>
</table>
| Data Preparation   | 1. Each transcribed word document was converted to .rtf file  
2. Each .rtf file was imported as P-document into AtlasTI (122 P-docs)                                                                 |
| First-level        | 1. Data were coded with a priori codes, developed from research, standardized measures, and online patient forums (i.e., confusion, orientation, short-term memory)  
2. For data that could not be coded with a priori codes, new codes were developed to ensure that all case study data were coded  
3. Coded data were sorted into categories, i.e., cognition, j-codes or “journal entry” codes and subcategories that became the raw units for subsequent thematic analysis  
4. A code book of all first-level codes was maintained with definitions for each code |
| Second-level       | 1. Each cognition-related first-level code within the 122 P-docs was sorted for and combined into the following documents:  
  “C-Attention + J-Decreased Attention-Focus,”  
  “C-Cognition,”  
  “C-Comprehension,”  
  “C-Concentration + J Decreased Concentration,”  
  “C-Confusion + J-Confusion,”  
  “C-Language + J-Altered Language,”  
  “C-Motor Function,”  
  “C-Orientation + J-Decreased Orientation,”  
  “C-Short Term Memory + J-Decreased Short Term Memory,”  
  “Fatigue + J-Mental Fatigue”  
2. These raw units of data were condensed into themes and patterns were identified (Miles & Huberman, 2014) |

Aim 2: Describe patient transient and residual cognitive symptoms as qualitatively reported by each patient’s care partner, and primary nurse during each hospital admission for IL-2 therapy. Qualitative data analysis for care partner and nurse journal entries, and care partner and primary nurse interviews for each case were analyzed using the same iterative process as described above (See Table 10) for patient
interviews using content analysis (Hsieh & Shannon, 2005) supported by the use of ATLAS.ti ("ATLAS.ti: Qualitative Software," 2014; Silver & Lewins, 2009).

**Aim 3:** Describe the trajectory of transient and residual cognitive symptoms in patients receiving IL-2 over the total number of hospitalizations, synthesizing patient data with care partner and nurse reports of symptom change. IL-2 case trajectories of cognitive symptoms were synthesized through a mixed-methods approach using visual overlays to plot a timeline of all treatment hospitalizations for each case, with data from aims 1 and 2 incorporated to allow for a visual representation over time. To describe the trajectories of cognitive symptoms, mean total scores from the patient standardized measures were graphed on a trajectory line within each case across the four hospitalizations. Qualitative data was incorporated into a table with the themes derived from the care partner and nurse observations of cognitive symptoms observed in the patient receiving IL-2. The research team then synthesized data with a written interpretive summary of the cognitive symptom trajectory within the IL-2 case to serve as a starting point for cross-case analysis. Because of the exploratory nature of this study, defining categories for grouping cases a priori was impossible; however, analysis within cases allowed for the emergence of salient cognitive symptoms (Miles & Huberman, 2014).
4.4.2 Cross-Case Analysis

To begin the cross-case analysis, trajectory lines (N=10) were created and visually inspected for patterns in patients’ cognitive symptoms. The research team created a matrix that grouped patients into the identified symptom trajectory category for each variable within the cognitive symptom domain, and qualitative data for cases within these groups were synthesized using interpretive summaries (Miles & Huberman, 2014). Pre- and post-treatment scores were compared to the qualitative data from these summaries for each hospitalization, compiling data from all data sources within the case.

4.5 Results

4.5.1 Demographics

See Table 1 for an overview of the study sample. Ten index participants were enrolled along with their ten care partners (eight spouses, one daughter, one significant other). 12 unique primary nurses were enrolled; several nurses served as the primary nurse for either multiple treatment hospitalizations for the same patient, or as the primary nurse for multiple index participants. Index participants’ age ranged from upper 30s to mid-60s. Care partners’ age ranged from early 30s to mid-60s. Care partners reported having anywhere between six to 38 years of familiarity with the patient. Primary nurses reported an average nursing experience of 12.2 years; the
newest nurse had a little over a year of nursing experience, while the most experienced nurse had almost 30 years of nursing experience.

Table 11: Demographic variables of case informants

<table>
<thead>
<tr>
<th>Case Informant</th>
<th>Gender</th>
<th>Race</th>
<th>Average Age (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (n)</td>
<td>F (n)</td>
<td>White (n)</td>
</tr>
<tr>
<td>Index Participant</td>
<td>8</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>(n = 10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Care Partner</td>
<td>1</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>(n = 10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Nurse</td>
<td>1</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>(n = 12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (n = 32)</td>
<td>10</td>
<td>22</td>
<td>28</td>
</tr>
</tbody>
</table>

12 doses were the maximum number of IL-2 doses that any of the patients received within a treatment hospitalization, while four was the minimum during a treatment hospitalization. Interestingly, despite what patients and care partners were told by providers and other healthcare professions, study results indicate that the number of IL-2 doses the index participant was able to tolerate was not an indication of whether the patient was responding well to treatment or if their follow-up CT scan would show disease improvement (See Table 12). For example, on average, patients who received only two cycles (because follow-up scans indicated disease progression after two treatment cycles) of treatment received more doses per treatment cycle in comparison to patients who received four treatment cycles.
Table 12: Number of IL-2 doses patients received by treatment cycle

<table>
<thead>
<tr>
<th>IL-2 Doses Received</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Cycle 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean of all Patients (n = 10)</td>
<td>8.7</td>
<td>5.5</td>
<td>6.75</td>
<td>5.75</td>
</tr>
<tr>
<td>Mean of Patients Completing Four Treatment Cycles (n = 4)</td>
<td>8.25</td>
<td>4.75</td>
<td>6.75</td>
<td>5.75</td>
</tr>
<tr>
<td>Mean of Patients Completing Two Treatment Cycles (n = 6)</td>
<td>9</td>
<td>6</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

4.5.2 Quantitative Cognitive Data

Cognitive data are graphically presented below to provide a visual representation of the data using mean total scores from all ten cases on the quantitative standardized measures (MoCA and AFI) at pre- and post-treatment for each hospitalization (treatment cycle). For treatment cycle 1 and cycle 2, n = 10. For treatment cycle 3 and cycle 4, n = 4.

On the MoCA (See Figure 6), post-treatment scores decreased in comparison to pre-treatment scores but improved with each subsequent treatment cycle. Scores ≥ 26 indicate individuals who are cognitively intact. Therefore, according to this measure, aside from cycle 1, patients receiving IL-2 remained cognitively intact.
Mean self-reported attention scores on the AFI decreased from pre- to post-treatment time points (See Figure 7), although patients returned to their baseline level between treatment cycles. The largest change in attention occurred during Cycle 4 of treatment. According to these quantitative measures, cognitive symptom alterations were transient, and there were no residual alterations, meaning that index participants returned to baseline prior to each cycle of treatment.
4.5.3 Case Exemplars

4.5.3.1 Selection of Case Exemplars

Because of the exploratory nature of this study, intrinsic case study was used to understand the phenomenon of cognitive symptoms patients receiving IL-2 experienced within and across treatment hospitalizations (Crowe et al., 2011). The research team sought to understand questions such as what the cognitive symptoms are that patients receiving IL-2 experience, when they appear, how they change over time, and the severity and duration of these symptoms. Three case exemplars were chosen from the ten IL-2 cases based on their uniqueness and richness of data (Crowe et al., 2011). Exemplars were selected from the cases that completed four treatment
hospitalizations because of the abundant, rich trajectory data captured through the cases that progressed through multiple treatment hospitalizations.

The study team compiled a priori definitions of each cognitive symptom (e.g. comprehension, confusion, orientation, concentration, attention, short-term memory, motor skills, speech, and fatigue) prior to data collection (See Figure 8). These a priori definitions were derived from prior research studies, the standardized measures, and online patient forums. After analyzing qualitative data (reports of symptoms observed by the care partner and nurses, and/or experienced by the patient receiving IL-2), the team formed a new a posteriori definition. In each case exemplar, scores on the standardized measures were compared with qualitative reports of symptoms experienced, and evidence is provided to support each a posteriori definition.
**Figure 1:** Final a posteriori definitions for each cognitive symptom.

* A Priori Definition: from codebook derived from prior studies, measurement scales, and patient forums.

** A Posteriori Definition: new formalized definition derived from data analysis.
4.5.3.2 Case Study: Exemplar 1

The index participant was a white male in his 60’s who had his wife as his care partner. The index participant received seven doses during cycle 1, five doses during cycle 2, seven doses during cycle 3, and four doses during cycle 4 of treatment. See Figure 9 for pre- and post-treatment total scores on the MoCA. The MoCA is a clinician-administered standardized measure that quantitatively evaluates global cognitive functioning, specifically visuospatial abilities, orientation, executive functioning, abstraction, attention, language, and short-term memory (Nasreddine et al., 2005). Although total scores on the MoCA reflect intact cognitive functioning at all time points except for pre-treatment for cycle 1 and post-treatment for cycle 3, the index participant, his care partner, and his primary nurse reported symptoms such as difficulty focusing, short-term memory alterations around the timing of rigors (excessive, severe shaking or convulsing), mumbled and slurred speech, an inability to multitask, and severe physical and mental fatigue.
See Figure 10 for pre- and post-treatment total scores on the Attentional Function Index. The AFI is a self-report measure that evaluates concentration, mental fatigue, cognitive alterations, and confusion (Cimprich et al., 2011). Total scores on the AFI suggested that the index participant experienced severe decreases in attentional function at the end of cycles 1 and 2 of treatment, although these symptoms were better managed in later treatment cycles. Similar to what the mean scores on the MoCA and AFI indicated, quantitative measures for exemplar 1 do not reflect any residual cognitive symptoms.
While scores on the standardized measures indicated minimal alterations in global cognitive functioning, reports from the patient receiving IL-2, his care partner, and the nurses paint an entirely different picture. Although not reflected through the standardized measures, this patient experienced alterations in short-term memory, fatigue, and language during all treatment cycles; alterations in attention and focus during cycles 1, 2, and 3 of treatment; and alterations in comprehension during cycle 2 of treatment. See Table 13 for qualitative reports of cognitive symptom change.

During cycle 1, the patient reported difficulty focusing. He also reported short-term memory alterations around the timing of his rigor episodes. Mumbled speech started shortly after he received his first dose of IL-2. Slurred speech occurred after
receiving Demerol. By dose 7, his speech was very slow, and according to his wife, was likely a product of his exhaustion. He experienced significant fatigue at dose 7, which was exacerbated by severe episodes of diarrhea. During cycle 2, the patient experienced severe “mental dullness” including altered sustained attention (i.e. requesting sentences to be repeated); decreased focus and an inability to multitask; altered memory where he was unable to recall medications he had received; and difficulty formulating thoughts and sentences. During cycle 3, the patient reported an inability to focus, short-term memory alterations (not knowing if he had received his IL-2 dose), altered language (occurring during and after his rigors and episodes of respiratory distress), and extreme fatigue (particularly around doses 4 and 5). The patient reported feeling emotionally exhausted. During cycle 4, the patient reported short-term memory alterations, stating he was unable to recall details. He said that he experienced larger gaps in his memory when his rigors were particularly bad. He also reported altered language (i.e. difficulty forming sentences, and constantly stuttering).
Table 13: Qualitative reports of cognitive symptom change from exemplar 1

<table>
<thead>
<tr>
<th>Treatment Cycle</th>
<th>Symptom</th>
<th>Quote/Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1</td>
<td>Attention + Focus</td>
<td>• Patient: “Once the infusions get going I feel a little lightheaded and it is kind of hard for me to focus. It's like all I can think about is what's going on” (136:9).</td>
</tr>
<tr>
<td></td>
<td>Short-term Memory</td>
<td>• Patient: reported decreased short-term memory, specifically during and after bad episodes of rigors (135:12).</td>
</tr>
<tr>
<td></td>
<td>Language</td>
<td>• Care Partner: mumbled speech starting with the first dose of IL-2 (130:15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Care Partner: slurled speech occurred after receiving Demerol (130:17); could have been a result of either the pro re nata (PRN) medication or the dose of IL-2.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Care Partner: slowed speech (dose 7) as a product of his immense exhaustion (130:19); related to horrible episodes of diarrhea, completely draining him of all energy (127:66).</td>
</tr>
<tr>
<td>Cycle 2</td>
<td>Comprehension</td>
<td>• Nurse: Patient asked her to repeat herself several times around dose 5 (131:2).</td>
</tr>
<tr>
<td></td>
<td>Short-term Memory</td>
<td>• Nurse: decreased short-term memory, patient was forgetful of conversations (129:19).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Care Partner: confirmed these reports of altered memory. She said, “Anyway that was when he started feeling like he was having chills before it ever started. And so when I- you know when I got back and I got into the room and he said, ‘I’m just so cold. I’m so cold. ’ And I said, ‘Well maybe we need to call the nurse.’ He goes, ‘No I already had my Demerol and all.’ So it must have been an hour later when when ah- or maybe it was forty- five minutes and she said, ‘So you still don’t want your Demerol?” And he goes, ‘No, you already gave it to me.’ She goes, ‘No, you told me you didn’t want it.’ And- and he goes, ‘Oh my gosh I remember now that you told me that.’ So here he was you know going through all this and he didn’t remember. And so then there were a couple of times when um, you know when we would say something and- or he would say, ‘I thought you were gonna ask- ask her for the Atarax.’ And I’d say, ‘Honey, I- I did and she brought you your Atarax, remember?’ So there was a little bit of that. Um last time I wasn’t as aware of it as he was going through it but after we got home something would be said and he says, ‘Yeah I’m not really sure if I remember that or not’ you know that kind of thing. So- so I think there is a little bit of an amnesia effect to all of this- all of this process” (134:21).</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>• Patient: made the decision to end treatment because of mental dullness. “I had that mental dullness. I just couldn’t concentrate. I couldn’t do anything. And I just- I had to call it. I said, ‘Time out, I’ve had enough.’ So- I guess I called it. I felt too beat up” (129:10).</td>
</tr>
<tr>
<td></td>
<td>Miscellaneous</td>
<td>• Patient: During cycle 2, the patient identified that he would get a headache with his rigors (135:14).</td>
</tr>
<tr>
<td>Cycle 3</td>
<td>Attention + Focus</td>
<td>• Patient: reported dulled senses and an inability to focus (129:12).</td>
</tr>
<tr>
<td></td>
<td>Short-term Memory</td>
<td>• Patient: reported altered short-term memory, not knowing if he had even received the treatment dose (134:22).</td>
</tr>
<tr>
<td>Cycle 4</td>
<td>Language</td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>----------</td>
<td></td>
</tr>
<tr>
<td>• Care Partner: after a severe episode of rigoring and having difficulty breathing, Ativan helped calm the patient down; his speech was very disjointed and he was stuttering; patient was emotionally exhausted and shaken up after severe rigor episodes (126:67).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>Language</td>
<td></td>
</tr>
<tr>
<td>• Care Partner: fatigue became very bad around doses 4 and 5; he had a headache he just couldn’t get rid of (127:86).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The symptom experience described above was not reflected in the patient’s standardized measures. The patient receiving IL-2 developed self-management strategies and learned how to identify when symptoms were about to occur. Learning about his unique symptom experience during cycle 1 helped him to seek intervention prior to the onset of his symptoms, which helped him manage the severity of his symptoms in later treatment cycles. The patient receiving IL-2 and his care partner worked together to manage his rigors. They would set an alarm after the IL-2 dose as a reminder to ask the nurse for morphine and heated blankets, so they could catch the rigors early. The patient noticed that rigors would begin soon after his hands became cold, and this almost acted as an “aura” for him. At this time, he would ask the nurse
for Demerol, and had formed a system to self-manage and minimize his rigor experience.

4.5.3.3 Case Study: Exemplar 2

The patient receiving IL-2 was a white male in his 50’s whose wife was his care partner. He received eight doses during cycle 1, four doses during cycle 2, five doses during cycle 3, and four doses during cycle 4 of treatment. See Figure 11 for pre- and post-treatment total scores on the MoCA. Total scores on the MoCA indicate that the patient receiving IL-2 remained cognitively intact over all treatment hospitalizations with negligible changes in total scores.
Figure 11: Total MoCA scores at pre- and post-treatment for each treatment hospitalization

See Figure 12 for pre- and post-treatment total scores on the AFI. With the exception of his cycle 3 post-treatment score, the patient receiving IL-2 experienced severe alterations in attentional function at post-treatment, although he returned to baseline prior to the start of each subsequent treatment cycle. Similar to what was reflected by mean scores on the MoCA and AFI, quantitative measures for exemplar 2 do not reflect any residual cognitive symptoms.
Figure 12: Total AFI scores at pre- and post-treatment for each treatment hospitalization

Similar to Exemplar 1, qualitative reports of symptom change tell a very different story than what is quantitatively depicted above. See Table 14 for qualitative reports of cognitive symptom change. During cycle 1, the patient noticed difficulty focusing and comprehending what people were saying. He felt like he was in a “daze.” By dose 6 he was extremely fatigued to the point that he was unable to focus long enough to urinate into the urinal. He experienced gaps in his memory surrounding conversations with his wife and altered speech around the timing of his rigors resulting from exhaustion, which presented during dose 7. During cycle 2, he experienced short-term memory alterations and confusion and argued that he had not received IL-2 doses that had been administered to him. He was unable to focus on conversations. His
slurred speech occurred much earlier this cycle, beginning at dose 1. Fatigue was much more severe, also occurring at dose 1, and his severe fatigue ultimately was the reason he ended treatment. During **cycle 3**, the patient reported decreased comprehension and focus, disorientation, and altered speech, particularly surrounding severe episodes of rigoring (doses 3, 4, 5). By dose 5, his speech was incomprehensible. Confusion occurred much earlier than during his previous treatment cycles. He also became very fatigued and was never able to fully recover from his rigors. During **cycle 4**, the patient reported very severe confusion. He was unable to remember his conversations or finish his sentences. The patient stated that his fatigue was the worst it had been so far and that it had started at dose 1. By the end of the dose, he was already down to 40-50% of his baseline energy level. His fatigue continued to worsen with each subsequent dose of IL-2.
## Table 14: Qualitative reports of cognitive symptom change from exemplar 2

<table>
<thead>
<tr>
<th>Treatment Cycle</th>
<th>Symptom</th>
<th>Quote/Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Comprehension</td>
<td>• Patient: stated he had difficulty comprehending what people were saying to him, difficulty paying attention, and trouble formulating a response worsening as treatment progressed (129:23).</td>
</tr>
<tr>
<td>Cycle 1</td>
<td></td>
<td>• Patient: “It was just kind of like you were in a daze while you were under the treatment. So it took you a while to process what people are saying to you, and generate a response. And there were times I couldn’t even generate a response. I was just so out of it. My wife ended up answering for me” (131:3).</td>
</tr>
<tr>
<td></td>
<td>Attention + Focus; Fatigue</td>
<td>• Care Partner: During dose 6, he had trouble focusing, experienced confusion (i.e. not coherent, difficulty urinating into urinal), and was very fatigued (129:27).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Care Partner: When trying to use the urinal, he was, “Unstable on his feet and not able to hold the urinal or concentrate long enough to finish peeing—or he was peeing all over himself. So a lot of it was just loss of focus too. He knew he had to go (to the bathroom) but once he started going he didn’t care how it got out” (129:26).</td>
</tr>
<tr>
<td>Short-term Memory</td>
<td>Patient: reported gaps in memory surrounding conversations with his wife (134:28).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Language</td>
<td>• Patient: Around dose 7, experienced slurred speech when he was rigoring; speech worsened with exhaustion (130:26).</td>
</tr>
<tr>
<td>Cycle 2</td>
<td>Attention + Focus; Fatigue</td>
<td>• Patient: identified decreased focus related to fatigue; stated that his focus was so bad that he would forget what people were saying to him (129:24).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Patient: Fatigue hit earlier during cycle 2, starting at dose 1 (130:29).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Patient: fatigue was one of the reason he ended treatment. “Ah the reason for stopping was I just couldn’t take it anymore because of all the increased vomiting, the increased fatigue, it was more than twice as bad as it was the first go around. (Starting) about right after the first dose. It lasted longer in between doses. When I had the first (cycle), it would hit and then it was gone and I felt okay until the next dose. With this second (cycle) I was still feeling bad at the time I’d be getting the next dose. I did not have energy (to walk in the halls)” (127:123).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Patient: Ended up having to use a urinal to urinate because he didn’t have the energy required to walk to the bathroom located in his room (127:124).</td>
</tr>
<tr>
<td>Short-term Memory; Confusion</td>
<td>Care Partner: Short-term memory alterations and confusion. “He will swear up and down that he either didn’t get something or did get something. And I’ll say, ‘No you didn’t.’ And he swore that he had thrown up some pills and I said, ‘You didn’t throw ’em up.’ He goes, ‘Yes I did I remember throwing ’em up.’ The nurse that was there goes, ‘I haven’t given you pills in a very long time. So you couldn’t have thrown ’em up.’ He was like, ‘Well I tasted it.’” (136:18).</td>
<td></td>
</tr>
<tr>
<td>Cycle 3</td>
<td>Language</td>
<td>• Care Partner: Slurred speech and mumbling presented earlier in the treatment cycle, starting at dose 1 (130:29), than it did during cycle 1, stating that he would start a sentence and wouldn’t be able to complete the sentence (135:29).</td>
</tr>
<tr>
<td>Cycle 3</td>
<td>Comprehension</td>
<td>• Patient: Difficulty comprehending what nurses were saying to him; attributed this to his decreased focus (131:5).</td>
</tr>
<tr>
<td>Cycle 3</td>
<td>Language; Confusion; Short-term Memory</td>
<td>• Care Partner: Very bad rigors during doses 4 and 5, taking an hour to get him “calm.” During this period (starting at dose 3), he had slurred speech, confusion, and decreased short-term memory. His speech has been very bad and she constantly had to ask him to repeat what he had said (133:7). His orientation was altered and he was very irritable beginning with dose 1 (133:8). By dose 5, his care partner couldn’t understand his slurred speech, he couldn’t focus on what the nurse was asking him to do and could not comprehend instructions. He was also disoriented to time. By this point he was sleeping the majority of the time, particularly after bad rigor episodes (133:9). The confusion hit him much sooner than previous during previous cycles (136:19).</td>
</tr>
<tr>
<td>Cycle 4</td>
<td>Fatigue</td>
<td>• Patient: Fatigue was very bad after the rigors; in between doses, his energy level never fully returned to normal (126:109/127:130). “The first two doses I this feeling of heat, I start to turn red and I’m very fatigued. Um the rigors eventually kick in and there’s no set times of when they’re gonna start. It seems like the very first time it’s hours- maybe five hours before they start. And each subsequent time it gets a little shorter. Um the first two times they weren’t nearly as bad and I thought that maybe this series it wasn’t gonna be as- as rough. But by the third one they were bad- bad again” (127:131).</td>
</tr>
<tr>
<td>Cycle 4</td>
<td>Confusion</td>
<td>• Care Partner: His confusion got really bad. “The confusion had gotten really bad. Then he was irritable right before the treatment started. He was rocking back and forth and didn’t remember things. You’d tell him something or he would start a sentence and wouldn’t finish, um those types of things” (136:27).</td>
</tr>
</tbody>
</table>
| Cycle 4 | Fatigue | • Patient: Fatigue started after dose 1. “Dose one was probably the worst. As far as fatigue, when I got the first dose I thought, ‘I’m not gonna be able to do but one dose of this.’ And then I thought, ‘Well I’ll try- I’ll just try to stick it out.’ But you know I couldn’t get out of the bed. I had to have my wife bring me the urinal for the side of the bed cause I couldn’t get up to go to the bathroom. I was burning up with- I don’t know if I had the fever or not but I certainly felt like it. I was sweating and I did- every time I’ve had those rigors and the shakes and all- I had ’em that time but oddly enough they were as bad as the times afterwards. The second dose I got um same symptoms, the fatigue had let up some. Um the rigors were worse however they had worked out a cocktail of the Morphine and Ativan and it seemed to work pretty good and it knocked me out. By the time I was getting to the fourth dose I was just sick as a dog throwing up a lot, high fever, and shakes even when I wasn’t having the rigors and just breaking out in a sweat and couldn’t- couldn’t even hardly make myself get out of bed. But I did get up and go to the restroom a couple
times. And a couple other times my wife had to bring me the- the urinal to the bed. Um, and progressively each it progressively got worse” (127:135).

• Patient: After dose 1, he was already down to 40-50% of his 100% energy level. “It’s not so much getting dizzy, it’s because you are so weak. It feels like your legs are gonna give out on you. Now I’d have to sit down five times just moving around the room. Sit on the bed one side, sit on the other and get there in steps” (127:137).

• Care Partner: His fatigue got worse as treatment went on. “Um he progressively went downhill. It seemed like after the second dose he had a little bit more energy but I think that’s just cause he slept through the night. Then as soon as the third dose started it just went downhill. He just kind of laid in bed from then on and had a hard time getting up to go to the bathroom or any of that stuff. Usually he’ll sit up and do stuff and he was like, ‘Hand me this, hand me that.’ And so um he was pretty- pretty exhausted” (127:138).

The nurse made an effort to manage the index participant’s rigors but had limited success. The patient said,

The symptoms I experienced were I would become extremely hot once they gave me the dose. Um at any point during that eight hours it was never the same. I would go into- it would feel like I was getting extremely cold. It would start at my feet, move up my body and I would start doing the shaking, have the rigors. Um they tried everything under the sun. The medicines they used to try and stop ‘em they all made me vomit. And even gave me stuff to prevent that but nothing seemed to work. So then what they started doing was eventually giving me stuff that would kind of knock me out, hopefully it would- I would sleep through it. But even that didn’t work. I still ended up throwing up every, single time and it was violent” (137:58).

By his third treatment cycle, the patient eventually came up with a strategy to manage his rigors. He reported, “(The) morphine and the Ativan that they were giving me at the same- same time and it helped but it still took me 45 minutes to an hour it seemed like to get (the rigors) to stop” (137:59).
Although not reflected on quantitative measures, qualitative reports from the patient and care partner suggest that the index participant experienced residual fatigue. During each subsequent treatment cycle, fatigue hit the patient harder and faster, suggesting that the index participant did not recover back to baseline between his treatment cycles.

4.5.3.4 Case Study Exemplar 3

The patient receiving IL-2 was a black female in her upper 40s who had her husband as her care partner. She received 11 doses during cycle 1, five doses during cycle 2, 10 doses during cycle 3, and 11 doses during cycle 4 of treatment. See Figure 13 for pre- and post-treatment total scores on the MoCA. Total scores on the MoCA show decreased global cognitive functioning at the post treatment time point for cycles 2, 3 and 4; however, cognitive function trended up (improved) over the four treatment cycles with slight fluctuations in total scores.
See Figure 14 for pre- and post-treatment total scores on the AFI. This patient did not complete the AFI at the cycle 4 post-treatment time point. In general, the patient did not report major alterations in attentional function as reported on the AFI. Similar to what was reflected by mean scores on the MoCA and AFI, quantitative measures for exemplar 3 do not reflect any residual cognitive symptoms.
Figure 14: Total AFI scores at pre- and post-treatment for each treatment hospitalization

See Table 15 for qualitative reports of cognitive symptom change. Most of the patient’s cognitive symptom reports relate to fatigue, which worsened to the point where case informants witnessed the index participant falling asleep mid-task or mid-sentence. During each treatment cycle, her fatigue presented earlier and rapidly became more severe over time. During cycle 1, the patient described slurred speech and identified in herself an inability to complete a full sentence. By the second day of treatment, she experienced severe fatigue, reporting that she was at 50% of her baseline energy level. During cycle 2, she reported difficulty focusing, which is different than what she reported on the self-report AFI. Fatigue started at dose two, earlier than during cycle 1, and hit her faster and more severely. By her fifth dose, she reported...
feeling physically and mentally drained. During cycle 3, she reported worsening fatigue, claiming that fatigue was her most severe symptom. She reported that by the third day of treatment she was operating at 20% of her baseline energy level. By cycle 4, the patient reported experiencing the worst fatigue thus far. She also reported having a headache that would not go away. By dose seven, the nurse noticed the patient would fall asleep during tasks. Her husband reported that cycle 4 was by far the worst in regards to fatigue, and with each cycle of treatment his wife’s fatigue substantially worsened.

Table 15: Qualitative reports of cognitive symptom change from exemplar 3

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Symptom</th>
<th>Quote/Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1</td>
<td>Language</td>
<td>• Patient: Described her altered speech as slurred; not able to complete a full sentence as treatment continued (130:41).</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>• Patient: Described her energy level as 50% of her baseline functioning by the second day. “I guess the more you do, the more energy you lose. I feel like a dump truck hit me but I say, I’m not giving up.” (127:141).</td>
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<td></td>
<td></td>
<td>• Patient: Experienced a headache with her rigors (126:145).</td>
</tr>
<tr>
<td>Cycle 2</td>
<td>Attention + Focus</td>
<td>• Nurse: Decreased focus; Reported needing to touch her to arouse her from her sleep—she was exhausted (135:35).</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>• Care Partner: Fatigue was noticeable starting at dose 2 (126:151); after the 5th dose she was totally physically and mentally drained (127:154).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Care Partner: Believed fatigue hit her faster and more severely because she hadn’t fully recovered from her first cycle of treatment; everything hit her much faster this time (127:150).</td>
</tr>
<tr>
<td>Cycle 3</td>
<td>Fatigue</td>
<td>• Patient: Exhaustion/fatigue was by far the most severe symptom. By the third day, the patient reported operating at 20% of her baseline energy level (127:159).</td>
</tr>
<tr>
<td>Cycle 4</td>
<td>Fatigue</td>
<td></td>
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<tr>
<td>• Care Partner: His wife experienced a headache from the very first dose; this continued throughout treatment (126:164).</td>
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<tr>
<td>• Nurse: Fatigue again was described as the most severe symptom. By dose 7, the patient would fall asleep during tasks and was unable to stay awake (126:181).</td>
<td></td>
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</tr>
<tr>
<td>• Patient: Described her fatigue. “It’s way, way down right now. I got to get it together. Because once I like— I did twelve and it just took a couple of days to get my body back to normal. But it takes a lot out of you. Once you pass nine” (127:171).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Care Partner: Believed cycle 4 to be the most severely fatigued he has seen his wife so far (127:173).</td>
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</tbody>
</table>

During cycle 1, very early in her course of treatment, the patient found that if she received morphine early enough, she would be able to minimize her rigors. She would remind the nurse, “‘Hey don’t forget after the dose I get the shakes real bad.’ So the last dose they gave—the eleventh dose, the nurse had the Morphine in her pocket and the warm blankets ready to go” (124:111).

Similar to exemplar 2, this index participant also experienced residual fatigue between treatment cycles. Her fatigue became progressively worse with each treatment cycle.

### 4.5.4 A Posteriori Definitions

Qualitative reports of cognitive symptom change over the course of treatment gave the study team a new understanding of each a priori symptom definition, and a formalized a posteriori definition for each code was formed (McKenna, Pajnkihar, & Murphy, 2014). Each a priori code definition from the original codebook was then compared to the new a posteriori code definition, derived from data analysis. For
example, “Decreased focus/concentration” was described as difficulty communicating thoughts, not being sharp, having a blunted mind or mental dullness, an inability to focus or multitask, typically worsening as treatment continues and oftentimes occurring around the timing of rigors, co-occurring in several instances with anxiety, forgetfulness or rigors, and self-managed by decreasing external stimuli.

Altered comprehension was re-defined as, “Difficulty retaining new information, processing information slowly and a request to repeat sentences.” One patient’s wife described her husband’s experience with slowed processing speed,

The first full day of doses [Tuesday], [he was] just a little less quick to respond. Not immediate responses. Then by Wednesday, it was just more delayed speech. I could just tell there was a delay in processing what I was saying versus how quickly it was coming out of his mouth. (130:3)

A care partner from a different case said, “As treatment continued, he had difficulty comprehending what people were saying to him, had difficulty paying attention and he had trouble formulating a response” (129:23). The patient reported,

It was kind of like you were in a daze while you were under the treatment. So it took you a while to process what people are saying to you, and generate a response. And there were times I couldn’t even generate a response. I was just so out of it. My wife ended up answering for me. (131:3).

Altered confusion and orientation were combined and re-defined as,

“Grogginess or having incoherent thoughts or communication, and/or not oriented to person, place, time or situation.” These symptoms occurred with the administration of
PRN medications, during or after severe rigoring, hypoxic events, or with memory alterations. One care partner described the index participant as follows: “He was slightly confused, trying to place a face balm bottle down, upside down with the rounded end down instead of the flat end” (127:50). A nurse reported that the patient’s confusion would occur after rigoring but in between the doses for a few hours. She said the patient was very tired, forgetful, and mentioned he was feeling out of it.

Altered focus, concentration, and attention were combined and re-defined as, “Not sharp, having a blunted mind, mental dullness, forgetfulness or difficulty communicating thoughts. An inability to focus or multitask, progressively worsening as treatment continues.” These symptoms often occurred around the time of rigors and with anxiety. The patient said that his processing was slower:

It was definitely tougher to follow things that were going on. If I really wanted to be engaged watching a TV show or something like that, it wasn’t happening. [The symptoms] got progressively worse as I got farther into treatment. So Thursday, which was yesterday, was the last day that I did any infusions and was far and away the worst. I was just completely out of it the entire day. I was exhausted and just not engaged and not just, yea. I was just shot. (129:1)

By the end of treatment, the patient reported,

Struggling with simple tasks that [I] should be able to do. Like responding to text message, or typing on a screen on a smart phone or on [my] laptop. [I] just couldn’t get through things. [I] could just tell that [I] was just not mentally all there (129:4).
The patient mentioned that he experienced difficulty concentrating. More specifically, the patient recalled,

Um, for me the biggest thing is having the ability to focus. Like my brain could not multi-task. So trying to do things...if there was somebody changing the trash, and the TV on, and someone taking my vitals, and a doctor asking me questions, my brain couldn't process all of those things. It is like, you really need one thing to do. (129:5)

Another care partner described her husband trying to use the urinal:

[He was] unstable on his feet and just not able to hold it and concentrate long enough to um- to finish peeing or he was peeing all over himself. So a lot of it was just loss of focus too. But he knew he had to go but once he started going he didn’t care how it got out. (129:26)

Altered short-term memory was re-defined as, “Lapses in memory,” which occurred with increased sleep, the administration of PRN medications, fatigue, and surrounding rigor episodes. Altered short-term memory worsened as treatment progressed. The nurse noted altered short-term memory towards the end of treatment around dose 10, “He didn't remember me hanging the bag. And then he thought that he had missed the rigors and chills. But they just hadn't come yet, and they came like 10 minutes after he asked if he had missed them” (134:1). Another care partner reported,

With his rigors, he experienced agitation, altered short-memory, and decreased orientation. His short-term memory was off. His orientation was off. He was talking about- at one point he said, ‘I’ve got to get dressed for the university game.’ I’m like, ‘You got to what?!’ At another point he was saying, ‘I think Sinatra (their cat) is in the bushes.’ And I was like, ‘You’re not at home. You are in the hospital.’ (124:123)
Altered motor skills were re-defined as, “Changes in hand-eye coordination, loss of dexterity and/or feelings of being wobbly or unstable on feet.” During cycle 1 of treatment, one care partner witnessed altered motor functioning towards the very end of treatment. She stated, “Yesterday morning before they decided to end treatment, he had dropped a Gatorade bottle, and it took him a minute to realize” (129:6). The patient added,

It was just kind of basic hand-eye coordination stuff. I was holding a Gatorade bottle. Just sitting there holding it and just dropped it out of my hand. Um, then took a minute to even realize that I had done it. The doctor came in and she asked me to touch her finger, touch my nose with the other hand and it was a little shaky” (132:2).

The index participant’s motor skills improved several hours after his final IL-2 dose. Another patient stated, “I would close my eyes, we would talk for a while and you’d say, ‘Here let me give this pen or pencil.’ And I would reach to the wrong place.” (123:18).

Altered language was re-defined as, “Slurred speech, decreased executive function, or mumbling, rambling or stuttering.” Altered language occurred around the timing of rigors and was potentially related to the administration of PRN medications, or thrush, pain or dry mouth. One index participant attributed his altered speech to thrush in his mouth, making it uncomfortable to talk, “I could tell that it was slurred.
And it was because of the infection and the pain in my mouth. I was actually apologizing to people, I can’t get this out, here is what I’m trying to say” (130:2).

Fatigue and exhaustion were combined and re-defined as, “Feelings of exhaustion or being beat-up resulting in being dizzy or light-headed.” These symptoms occurred along with decreased appetite, decreased concentration, and mental dullness, and presented during or after a severe episode of rigoring.

One care partner reported her husband sleeping 20 hours a day. She said, He tried to stay awake and watch football, and he just couldn’t. And he was just passed out the whole day. He just looked really tired and looked like he didn’t sleep all night. So that fatigue. And then as the days went on, those symptoms just got more noticeable. He was barely able to keep his eyes open, sleeping the whole day. He just wasn’t able to keep his eyes open or have conversation. (126:3)

According to his wife, he felt the most “beat up” after dose 8 and she could clearly see a “difference in his increased sleep, fatigue and attention span. On day one of treatment [Monday], he was walking the halls. By Wednesday, he wasn’t able to really stay awake and did not walk the halls. This pattern of fatigue continued to worsened throughout the duration of his treatment” (126:6).

The study team developed no a priori definition for managing cognitive changes; however, patients and care partners managed cognitive symptoms by “Getting rid of excess stimuli (i.e. turning TV off, putting away books), and/or taking an IL-2 dose off or skipping a dose of treatment.”
4.6 Discussion

Many of the cognitive symptoms verbally reported by the patients receiving IL-2, their care partners, their primary nurses and/or nurses were not captured by the standardized measures. Perhaps this is one of the reasons why cognitive symptoms often go unidentified and unmanaged in the IL-2 patient population. This exploratory mixed-method case study illuminated the importance of case study research in this population and substantiated the beneficial utility of gathering data from multiple case informants when the patient receiving IL-2 was unable to self-identify symptoms he/she was experiencing during treatment.

Severe fatigue existed in nearly all patients receiving IL-2. Fatigue typically co-occurred with and was directly related to attentional function. That is, as fatigue worsened, so did the patient’s ability to focus and finish tasks. The concept of “attentional fatigue” has been identified in the breast cancer population; breast cancer patients reported difficulty completing tasks and problem solving because of their level of fatigue (Von Ah et al., 2017). Perhaps PRN medications contributed to feelings of fatigue, and a focus on fatigue management is important because several patients reported such severe fatigue during treatment cycles that they ultimately decided to end treatment because they felt they were unable to tolerate any additional doses.
Several patients and their care partners reported that they were told that patients who receive more doses of treatment have a better response to the treatment. Of similar note, patients and care partners were also educated that patients who experience more severe “flu-like” symptoms (indicative of a cytokine storm) during treatment responded better. Patients reported experiencing added stress and fear related to this inaccurate information. Patients often set expectations, which were sometime unattainable, surrounding how many doses they “needed to receive” to initiate a response. Feelings of failure resulted in patients who did not receive their goal number of IL-2 doses.

Short-term memory and confusion co-occurred, and memory alterations occurred during or around the time of a confused mental state. The severity of these cognitive symptoms was associated with the severity of the index participant’s rigors. If the patient receiving IL-2 had a very bad experience with rigors, he also would experience more severe cognitive symptoms.

The qualitative component of this study was crucial for the development of new cognitive symptom definitions, as well as modifying previous symptom definitions. Indeed, these symptoms would have been overlooked and consequently gone unidentified if the index participant was evaluated with standardized measures alone. This case study highlighted the importance of qualitative reports to not only identify
cognitive symptoms, but also to understand their frequency, duration, severity, and change over the treatment trajectory. Qualitative research is important for making progress towards translational research and the development of interventions specific to these patients, thus turning research into clinical practice (Florczak, 2017).

The care partner was invaluable in identifying and helping manage cognitive alterations across the course of treatment. Although cognitive symptoms related to IL-2 treatment may not be eliminated, future interventions can be developed to help patients, care partners, and nurses manage these symptoms to improve the patient’s quality of life and treatment adherence (Capuron et al., 2002; Petrulio et al., 2007; Tarhini et al., 2007). While some interventions will target the patient, others will focus on the patient, care partner dyad, and the healthcare team.

Future interventions can target education for the patient and care partner prior to hospital admission for IL-2 treatment. Education about the illness trajectory and what to expect during and after treatment has been shown to help care partners and patients set realistic shared expectations, improve coping, and decrease feelings of powerlessness (Guo et al., 2013; Northouse, Katapodi, Song, Zhang, & Mood, 2010; Williams, 2007). Although, most research focuses on patient interventions, care partner interventions have been found to not only help the care partner but also benefit the patient by decreasing negative outcomes (Guo et al., 2013).
Providers who identify changes in the patient’s trajectory can make appropriate referrals earlier in the patient’s treatment phase to better assist the patient receiving IL-2 (Smith & Liehr, 2014a). Interventions directed at the patient can target treatment-emergent or residual symptoms, and can include both pharmacological and non-pharmacological interventions, which can be initiated by either the provider, care partner, or patient.

Equally important, interventions can also target the patient/care partner dyad with the goal to build a long lasting, strong relationship while reducing the negative outcomes that care partners frequently experience but oftentimes are overlooked. Care partners and patients experience extreme distress after a cancer diagnosis, and social workers are beneficial in facilitating communication, making referrals for housing and home equipment, and meeting many other psychosocial needs of the dyad. Additionally, education can be provided to the healthcare team about cognitive symptoms to assess for that may go unnoticed on standardized metrics, as well as increasing communication among the healthcare team, patient, and care partner.

Previous studies investigating the cognitive symptoms of patients receiving IL-2 that included a qualitative research component or utilized a case study approach to assess for symptoms over the treatment trajectory were unavailable in the literature. This study highlighted that researchers and clinicians may have been missing the target
regarding the cognitive symptom challenges that patients receiving IL-2 experience, which is one of the reasons why patients report that these very challenging cognitive symptoms often go unmanaged. Likely, other cancer patient populations who are receiving aggressive treatment also experience cognitive symptoms that remain unidentified and unmanaged. This mixed-method case study approach can also be applied to other patient populations where individuals undergo aggressive treatment for life-limiting chronic illnesses.
5. Trajectory of Affective and Sleep Symptoms in Patients Receiving High-Dose Interleukin-2 Therapy

5.1 Background

See Chapter 4 for background on high-dose Interleukin-2 (IL-2) and metastatic renal cell carcinoma (MRCC) statistics. Affective and sleep disturbance symptoms are prevalent in the cancer population, and these symptoms profoundly impact quality of life and treatment adherence. Affective symptoms include mood alterations, depression, anxiety, aggression, and suicidal ideation (Mavroukakis et al., 2001; Muehlbauer & White, 1998; Myint et al., 2009; The American Psychiatric Textbook of Neuropsychiatry, 1999). In a meta-analysis pooling symptom findings from 21 studies, which involved 4,067 cancer patients receiving active treatment for cancers of multiple origins, researchers reported that approximately 35% experience depression or sadness, 42% experience nervousness, and 52% experience irritability (Reilly et al., 2013).

Sleep disturbance symptoms include insomnia (initial, middle, delayed) and hypersomnia (Absolon et al., 2014). Researchers have reported that up to 80% of all cancer patients experience altered sleep while receiving aggressive treatment for their cancer (Spiegel & Riba, 2015). In the same meta-analysis described above, researchers reported that approximately 49% of cancer patients experience insomnia (Reilly et al., 2013). Furthermore, insomnia and sleep disturbance symptoms were reported as the second most common symptom (behind fatigue) (Reilly et al., 2013).
While some affective and sleep disturbance symptoms are transient, lasting a short duration during treatment (e.g. hallucinations), other symptoms may have residual effects, persisting after treatment has ended (e.g. anxiety, insomnia). For example, over 20% of cancer patients report anxiety symptoms at the 12-month post-treatment time point (Yi & Syrjala, 2017). Unfortunately, patients receiving immunotherapy also experience affective and sleep disturbance symptoms, and because these alterations can have lasting effects, it is important for researchers to study the symptom trajectory during and after treatment to better understand what symptoms occur and how they change over time.

Studying the trajectory of affective and sleep disturbance symptoms that patients receiving IL-2 therapy for renal cell carcinoma experience within and over hospitalizations using a case study approach is important because these symptoms change over time and have unique patterns and characteristics within individuals (J. P. Dutcher et al., 2014). A better understanding of when these symptoms arise, patterns in how they cluster and change over time, and their duration is critical to the design and testing of interventions that could alleviate these treatment-limiting symptoms.

Therefore, the purpose of this report is to describe the trajectory of affective and sleep disturbance symptoms that patients receiving IL-2 for renal cell carcinoma experience within and across hospitalizations. The research team followed a total of ten
IL-2 cases for up to four hospitalizations for IL-2 therapy. Three case exemplars with unique characteristics and attributes were chosen to best exemplify the trajectory of the IL-2 affective and sleep disturbance symptom experience over the treatment course. The specific aims of this study were to:

- **Aim 1**: Describe transient and residual affective (depression, anxiety, mood alterations) and sleep disturbance (insomnia, hypersomnia) symptoms in patients receiving IL-2 during up to four hospitalizations for IL-2 therapy.

- **Aim 2**: Describe transient and residual affective and sleep disturbance symptoms as qualitatively reported by each patient’s care partner and primary nurse during each hospital admission for IL-2 therapy.

- **Aim 3**: Describe the trajectory of transient and residual affective and sleep disturbance symptoms in patients receiving IL-2 over the total number of hospitalizations, synthesizing patient data with care partner and nurse reports of symptom change.

### 5.2 Methods

#### 5.2.1 Design

See Chapter 4 for a description of the research design.
5.2.2 Setting

See Chapter 4 for a description of the research setting.

5.2.3 Sample

See Chapter 4 for a description of the study sample (inclusion and exclusion criteria for the patient receiving IL-2, care partner, primary nurse, and nurses).

5.2.4 Instruments and Measures, and Data Collection Time Points

5.2.4.1 Standardized Measures

Affective and sleep symptom alterations in the patient receiving IL-2 were measured with four standardized measures (see Table 16) for overview of the measurement tools, who completed the tools, and the data collection time points) at two time points for each hospitalization: before the first IL-2 dose (pre-treatment) and immediately after the last dose (post-treatment) of IL-2. Standardized measures included the Hamilton Anxiety Rating Scale (HAM-A) (Hahn, 2007; Maier et al., 1988), the Inventory of Depressive Symptomatology–Clinician (IDS-C) (Bernstein et al., 2010; Rush et al., 2006; Rush et al., 2005), the eight-item Patient-Reported Outcomes Measurement Information System-Anxiety (PROMIS-8A) (Quach et al., 2016), and the eight-item Patient-Reported Outcomes Measurement Information System-Depression (PROMIS-8B) (Quach et al., 2016). Pre-treatment scores on these standardized measures collected at the time of each hospital admission were used as a baseline and compared to post-
treatment scores to assess affective and sleep disturbance symptom change and symptom trajectories for each case.

The IDS-C included a subscale measuring sleep disturbance (initial, middle, and delayed insomnia, and hypersomnia) symptoms. The research team used this subscale to evaluate sleep disturbance symptoms in patients receiving IL-2 and collected additional qualitative data about sleep disturbance systems through interviews.

### Table 16: Affective and sleep assessment measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Details, Variables, Psychometric Properties, and Data Collection Time Points</th>
</tr>
</thead>
</table>
| Demographic Data Questionnaire + Electronic Medical Record | • Race, gender, age, marital status, cancer staging, and treatments prior to IL-2 therapy  
• Collected through an enrollment questionnaire  
• Collected through a chart review of the electronic medical record |
| Quantitative—Completed by the Patient receiving IL-2 at Pre- and Post-treatment |
| HAM-A Hamilton Anxiety Rating Scale | • 14 item, investigator-administered questionnaire  
• Comprehensively measures anxiety symptoms  
• High internal consistency (α=0.77-0.92) (Maier et al., 1988).  
• Scoring:  
  - Each item rated from 0-4; 0 = symptom not present, 4 = very severe symptom severity  
  - Scores 0-17 = mild anxiety symptom severity; Scores 18-24 = mild to moderate severity; Scores 25-30 = moderate to severe severity |
PROMIS-8A
Patient-Reported Outcomes Measurement Information System-Anxiety
• 8 items measuring self-reported anxiety
  ○ Score ranging from 1 to 5 per item; Total score of 8 = no self-reported anxiety symptoms; Total score of 40 = maximum self-reported anxiety symptoms
  ○ High reliability (α=0.90) (Quach et al., 2016)

PROMIS-8B
Patient-Reported Outcomes Measurement Information System-Depression
• 8 items measuring self-reported depressive symptoms
• Scoring:
  ○ Score ranging from 1 to 5 per item; Total score of 8 = no self-reported depressive symptoms; Total score of 40 = maximum self-reported depressive symptoms
  ○ High reliability (α=0.91) (Quach et al., 2016).

Qualitative Journal Entry—Completed by Care Partner and Nurse(s) at Pre-treatment and time of each IL-2 dose
Investigator developed semi-structured journal
• Semi-structured journal entry containing a checklist of symptoms observed in the patient receiving IL-2, followed by an open-ended prompt asking for expansion on symptoms witnessed in patient.

Qualitative Interview—Completed by Patient receiving IL-2, Care Partner and Primary nurse at Post-treatment
Investigator developed interview guide
• In depth, recorded, semi-structured interview to explore and describe the trajectory of transient and residual IL-2—induced affective + sleep disturbance symptoms witnessed in or experienced by the patient receiving IL-2.

See Figure 15 for a model illustrating the longitudinal data collected from each case informant over each treatment hospitalization using a case study approach to understand the trajectory of affective and sleep disturbance symptoms experienced by or observed in the patient receiving IL-2.
5.2.4.2 Semi-Structured Journal

See Chapter 4 for a description of the semi-structured journal. Specific affective and sleep disturbance symptoms on the checklist included increased depression, increased anxiety, mood alterations, sleep disturbances, hallucinations, increased sleep, decreased sleep, increased happiness, and increased irritability.

5.2.4.3 Semi-Structured Interview

Recorded semi-structured interviews were used to explore and describe the affective and sleep disturbance symptom experience observed in or by the patient receiving...
IL-2. See Chapter 4 for a description of the semi-structured interview with each case informant.

5.3 Procedures

5.3.1 Recruiting and Consenting

See Chapter 4 for a description of the recruiting and consenting procedures.

5.3.2 Data Collection Procedures

After hospital admission, the patient scheduled to receive IL-2 completed four standardized measures evaluating baseline affective and sleep disturbance symptoms: two self-report (PROMIS 8A and PROMIS 8B) measures and two investigator-administered (HAM-A and IDS-C) measures. These measures were repeated again after the last dose of IL-2, and this pattern of data collection was repeated for each of the subsequent treatment hospitalizations that the patient completed. See Chapter 4 for a description of study procedures.

5.4 Data Analysis

Refer to Chapter 4 for an overview of data analysis. Detailed below are specifics related only to analysis of affective and sleep disturbance symptoms. Data preparation occurred prior to data analysis. Individual scores for each item on the standardized measures (HAM-A, IDS-C, PROMIS-8A, PROMIS-8B) and scores for each item on the sleep disturbance subscale (from the IDS-C) were entered into an Excel spreadsheet.
5.4.1 Within-Case Analysis

Analysis of each case began with a description of demographic variables (See Table 11 in Chapter 4). **Aim 1:** Describe transient and residual affective (depression, anxiety, mood alterations), and sleep disturbance (insomnia, hypersomnia) symptoms in patients receiving IL-2 during up to four hospitalizations for IL-2 therapy. For quantitative data analysis of the total study sample, total scores from the four standardized measures (HAM-A, IDS-C, PROMIS-8A, PROMIS-8B) and the sleep subscale (from the IDS-C) administered to the patient receiving IL-2 were scored at pre- and post-treatment time points for each hospitalization to assess for alterations in affect and sleep disturbance. The mean total score for the four standardized measures (HAM-A, IDS-C, PROMIS-8A, PROMIS-8B) and sleep subscale (from the IDS-C) for the ten patients receiving IL-2 were mapped on a graph at pre- and post-treatment for each cycle for visual inspection to understand the study sample as whole and to visually analyze which affective and sleep disturbance symptoms appeared over the treatment trajectory (Onwuegbuzie & Dickinson, 2008). For quantitative data analysis of each individual case, after graphing mean scores for the study sample, total scores for each patient receiving IL-2 were individually graphed using the same technique described above. Pre-treatment total scores on the standardized measures for each hospitalization were compared over all hospitalizations to further assess for long-term symptoms in
each patient receiving IL-2. For example, pre-treatment scores on the HAM-A (measuring “anxiety”) for hospitalizations 1, 2, 3, and 4 were compared to determine if the patient returned to his/her baseline anxiety level prior to the next treatment hospitalization. For qualitative data analysis, patient interviews for each case were analyzed using content analysis (Hsieh & Shannon, 2005) supported by the use of ATLAS.ti ("ATLAS.ti: Qualitative Software," 2014; Silver & Lewins, 2009). See Table 17 for detail about qualitative data analyses.
Table 17: Qualitative data analysis using content analysis

<table>
<thead>
<tr>
<th>Coding Level</th>
<th>Process</th>
</tr>
</thead>
</table>
| Data Preparation | 3. Each transcribed word document was converted to a .rtf file  
4. Each .rtf file was imported as a P-document into AtlasTI (122 P-docs) |
| First-level | 5. Data were coded with a priori codes, developed from research, standardized measures, and online patient forums (i.e., depression, anxiety, hypersomnia)  
6. For data that could not be coded with a priori codes, new codes were developed to ensure all case study data were coded  
7. Coded data were sorted into categories, i.e., affective, sleep, j-codes or “journal entry” codes, etc. and subcategories that became the raw units for subsequent thematic analysis  
8. A code book of all first-level codes was maintained with definitions for each code |
| Second-level | 3. Each affective- and sleep-related first-level code within the 122 P-docs was sorted for and combined into the following documents: “Anxiety,” “Irritability + Aggressiveness,” “Depression + Hallucinations + Mood Alterations,” “All Sleep Codes”  
4. Codes were merged: Ex. “Irritability” and “Agitation” were merged into “Irritability/Agitation” because these codes co-occurred and patients and their care partners often used similar definitions for both of the codes  
5. New codes were created: Ex. “X-General Anxiety” by merging the following codes: “X-Anxiety r/t Scan,” “X-Anxiety r/t the Unknown,” “X-Anxiety Unknown Origin,” and “X-Variability”  
6. These raw units of data were then condensed into themes and patterns were identified (Miles & Huberman, 2014) |

**Aim 2**: Describe patient transient and residual affective and sleep disturbance symptoms as qualitatively reported by each patient’s care partner, and primary nurse during each hospital admission for IL-2 therapy. Qualitative data analysis for care partner and nurse journal entries, and care partner and primary nurse interviews for each case were analyzed using the same iterative process as described above for patient
Aim 3: Describe the trajectory of transient and residual affective and sleep disturbance symptoms in patients receiving IL-2 over the total number of hospitalizations, synthesizing patient data with care partner and nurse reports of symptom change. IL-2 case trajectories of affective and sleep disturbance symptoms were synthesized through a mixed-methods approach using visual overlays to plot a timeline of treatment doses and all hospitalizations for each case, with data from aims 1 and 2 incorporated in order to create a visual representation over time. To describe the trajectories of affective and sleep disturbance symptoms, mean total scores from the patient standardized measures were graphed on a trajectory line within each case across the four hospitalizations. Qualitative data was incorporated in a table with the themes derived from the care partner and nurse observations of affective and sleep disturbance symptoms observed in the patient receiving IL-2. The research team analyzed each case and created a written interpretive summary of the affective and sleep disturbance symptom trajectory, which was the starting point for cross-case analysis. Because of the exploratory nature of this study, defining categories for grouping cases a priori was not possible; however, analysis within cases allowed for salient observations in regards to affective and sleep disturbance symptoms (Miles & Huberman, 2014).
5.4.2 Cross-Case Analysis

To begin the cross-case analysis, the study team created trajectory lines (N=10) and examined them for patterns in patients’ affective and sleep symptoms. Researchers then created a matrix that grouped patients into the identified symptom trajectory category for each variable within the affective and sleep symptom domains and synthesized qualitative data for cases within these groups using interpretive summaries (Miles & Huberman, 2014). Pre- and post-treatment scores were compared to the qualitative data from these summaries for each hospitalization, compiling data from all data sources within the case.

5.5 Results

5.5.1 Demographics

See Chapter 4 for detail about the study sample and demographic variables for the case informants. Also see Chapter 4 for a description of the mean number of IL-2 doses received by patients for each treatment cycle.

5.5.2 Quantitative Affective and Sleep Disturbance Data

Affective and sleep disturbance data are graphically presented below to provide a visual representation of the data using mean total scores from all ten cases on the quantitative standardized measures (HAM-A, IDS-C, ISC-C Sleep Subscale, PROMIS-
8A, and PROMIS-8B) at pre- and post-treatment for each hospitalization (treatment cycle). For treatment cycle 1 and cycle 2, n = 10. For treatment cycle 3 and cycle 4, n = 4.

5.5.2.1 Affective Data

Mean total scores on the IDS-C (See Figure 16) increased from the “normal” to the “mild” depressive symptom range across all treatment cycles when comparing mean pre-treatment scores to mean post-treatment scores, suggesting transient depressive symptoms within treatment hospitalizations. On average, patients started with slightly higher depressive scores for each subsequent treatment cycle, suggesting mild residual depressive symptoms across treatment hospitalizations; however, this slight increase in depressive symptoms is negligible.
Figure 16: Mean total IDS-C scores at pre- and post-treatment for each treatment hospitalization

Mean scores on the self-reported, short-form PROMIS-8B standardized measure (See Figure 17) did not reflect changes in depressive symptoms from pre- to post-treatment, nor across treatment hospitalizations, which shows a very different trend than what is depicted by mean IDS-C scores.
Although mean anxiety scores on the HAM-A indicate worsening anxiety symptoms from pre- to post-treatment for each treatment hospitalization (See Figure 18), these scores were always classified as “mild,” and the most severe anxiety symptoms were experienced during cycles 1 and 4 of treatment. Mean quantitative scores on the HAM-A suggest that index participants did not experience residual anxiety symptoms, and patients returned to baseline between treatment cycles. Interestingly, severe anticipatory anxiety levels were qualitatively reported by several IL-2 cases (see exemplars below). Scores on the HAM-A did not reflect the anxiety symptom experience of these patients, as the HAM-A did not assess anticipatory anxiety.
Mean scores on the self-reported short-form PROMIS-8A standardized measure (See Figure 19) indicated that anxiety symptoms trend down across the four treatment hospitalizations, although similar to the PROMIS-8B, minimal change in anxiety symptoms are reflected in mean scores from pre- to post-treatment and across treatment hospitalizations.
5.5.2.2 Sleep Disturbance Data

Sleep disturbance symptoms (insomnias, hypersomnia) as reported on the IDS-C Sleep Disturbance Subscale worsened from pre- to post-treatment (See Figure 20) and were the worst after Cycle 4.
5.5.2.3 Clinician-Rated versus Self-Reported Short Form Data

Self-reported, short-form PROMIS-8A and PROMIS-8B measures did not depict changes identified by the clinician-rated measures. For example, the IDS-C and the PROMIS-8B are both standardized measures that evaluate depressive symptoms. The large increases in depressive symptoms shown on the IDS-C from pre- to post-treatment were not reflected on the PROMIS-8B (See Figure 21). Importantly, sleep alterations were captured on the IDS-C, but not the PROMIS-8B, and were found to severely impact patients receiving IL-2.

Figure 10: Mean sleep disturbance symptom scores on the IDS-C Sleep Subscale at pre- and post-treatment for each treatment hospitalization
Anxiety symptom trends look vastly different on the clinician-rated HAM-A measure in comparison to the self-report short-form PROMIS-8A measure across treatment hospitalizations.
5.5.3 Case Exemplars

5.5.3.1 Selection of Case Exemplars

See Chapter 4 for a description of how the case exemplars were selected. The study team formed a priori definitions for each affective symptom (e.g. anxiety, depression, irritability, and hallucinations) and sleep disturbance symptom (e.g. initial, middle, and delayed insomnia, and hypersomnia) prior to data collection (See Figures 23 and 24). A priori definitions were derived from prior research studies, standardized measures, and online patient forums. After analyzing qualitative data (reports of symptoms observed by the care partner and nurses, and/or experienced by the patient receiving IL-2), the team formed a new a posteriori definition. In each case exemplar, scores on the standardized measures were compared with qualitative reports of symptoms experienced, and evidence is provided to support each a posteriori definition.
Figure 13: Final a posteriori definitions for each affective symptom

*Prior Definition: from codebook derived from prior studies, measurement scales, and patient forums.
**A Posteriori Definition: new formalized definition derived from data analysis.
5.5.3.2 Case Study: Exemplar 1

The index participant was a white male in his 60’s who had his wife as his care partner. This patient received seven doses during cycle 1, five doses during cycle 2, five doses during cycle 3, and four doses during cycle 4 of treatment. See Figure 25 for pre- and post-treatment depressive symptom scores. While the PROMIS-8B was insensitive to depressive symptom change, the IDS-C indicated a large increase in depressive symptoms from pre- to post-treatment, increasing from “normal” to the “mild to
moderate” depressive symptom range after cycle 1 of treatment. Post-treatment depressive symptom scores trended down and were lower at the end of cycle 4 in comparison to cycle 1. Scores on the IDS-C suggest that while the index participant for exemplar 1 did not experience residual depressive symptoms across treatment hospitalizations, he did experience transient depressive symptoms within each treatment hospitalization.

![Exemplar 1: Depressive Symptom Total Scores](image)

**Figure 15: Total depressive symptom scores at pre- and post-treatment for each treatment hospitalization**

See Figure 26 for pre- and post-treatment sleep disturbance symptom scores. As indicated by higher scores, this patient experienced severe sleep disturbance symptoms.
at the end of cycle 1 and cycle 4 of treatment; however, sleep disturbance symptoms returned to baseline before each subsequent treatment cycle.

See Figure 27 for pre- and post-treatment anxiety scores. Interestingly, the patient receiving IL-2 self-identified anxiety symptoms at pre- and post-treatment of cycle 1, but his anxiety decreased across the remaining treatment cycles, according to PROMIS-8A results. The clinician-rated HAM-A identified increased anxiety at the end of each treatment cycle, but anxiety symptoms returned to baseline prior to the start of each subsequent treatment cycle. The self-reported PROMIS-8A and the clinician-rated HAM-A showed very different trends in anxiety symptoms over the treatment course, which may be related to their psychometric characteristics and capturing of different anxiety symptom content.
See Table 18 for qualitative reports of affective and sleep disturbance symptoms observed in or experienced by the patient receiving IL-2. Anxiety became a recurrent theme and was prominent in cycle 1 and cycle 2 of treatment, particularly the “anticipatory anxiety” surrounding the timing of the index participant’s rigors. If the patient receiving IL-2 had a very severe recent episode of rigors, his anxiety was higher. His level of anxiety fluctuated based on newly acquired knowledge and his previous experiences. At the time of his hospital admission for cycle 2, his wife stated that she identified depressive symptoms in her husband after the first cycle of treatment when they were discharged to home. Her husband did not want to leave the house or see people until about a week and a half after treatment ended. As cycle 2 of treatment
continued, he became more withdrawn and flat. Although he had lower anxiety levels during cycle 2 because he knew what to expect, he still had anticipatory anxiety surrounding the timing of his rigors. He was anxious about receiving Demerol because he remembered getting confused and urinating in a trashcan. He was also anxious because of the variability in provider communication (i.e. one provider would call IL-2 a chemotherapy while another would classify the drug as an immunotherapy). His sleep disturbances typically presented as decreased or restless sleep towards the beginning of the treatment hospitalization, but by the end of the treatment cycle, the patient was sleeping most of the day, in a state of hypersomnia.
Table 18: Qualitative reports of affective and sleep disturbance symptom change from exemplar 1

<table>
<thead>
<tr>
<th>Treatment Cycle</th>
<th>Symptom</th>
<th>Quote/Evidence</th>
</tr>
</thead>
</table>
| Cycle 1         | Anxiety               | • Care Partner: Noted anticipatory anxiety before dose 1 because of how severe he was told the rigors could be (124:5).  
• Patient: Described anticipatory anxiety surrounding “how miserable (the treatment) makes you feel” (124:2).  
• Care Partner: Anxiety surrounding his rigors; anxiety increased and decreased based on the severity of the rigors in each previous dose. “He has always been one that if he gets a fever or the flu, he gets really bad chills. Coming in we knew that was a major side effect. Everybody had agreed on that one side effect if nothing else, that 90-some percent of patients get (rigors). So he was very anxious about that side effect in particular. Everything else he felt like he was going to be able to manage and he could do his part, but that one made him extremely nervous. Then, the second day...he experienced it with the first treatment, and then he did not have it with the second and third treatment. So he calmed down some, then the fourth and fifth treatment, it was pretty violent after both treatments. So that’s when his anxiety level started to rise a little. I could tell that he was starting to dread the next treatment because he knew that was coming. It was almost like he was making them worse because he was so anxious about it happening, whether or not it was going to happen. But once they were able to control it, they would give him medication and within about 30 minutes he would calm down” (124:4).  
• Patient: Anxiety improved as he moved “away from treatment time” (124:17).  
• Care Partner: Fluctuations in anxiety. “On one hand, he’s probably dreading it more, but on the other hand, anxiety wise he at least knows what to expect. So I know he will be dreading it. I know he will be hating life when the (date) gets here, but I think he will be a little more prepared as to he knows what’s to happen” (124:18). |
|                 | Decreased Sleep; Language | • Care Partner: Talking in his sleep which he never does; her husband was very restless, which she thought may have been related to PRN Demerol (126:23).  
• Care Partner: Restlessness continued to progress; began mumbling in his sleep by dose 7 (126:25) |
| Cycle 2         | Depressive             | • Care Partner: Depressive symptoms after his first cycle of treatment when they returned home from the hospital. “He didn’t feel like doing anything. He didn’t feel like getting out of the house. He didn’t want to see people. He really didn’t have any desire to get out or go anywhere or do anything. It will probably be the middle of next week before he tries to venture out” (123:1).  
• Care Partner: As treatment continued, “He got more of that withdrawn, flat, but I honestly I couldn’t put it all on if it was from the IL-2 or if it was from his anxiety related to, umm, like a fight or flight almost. Like he was doing all he could do to answer the question I asked him” (123:2). |
| Anxiety                                                                 | • Patient: Lower anxiety coming back for cycle 2 of treatment because he knew what to expect (124:3).  
|                                                                      | • Care Partner: Anticipatory anxiety surrounding the rigors. “He was still dreading the rigors, but he knew what to expect. We talked about it many times, but it is sort of like having a baby. Is it worse the first time because you don’t know what’s going to happen or is it worse the second time because you do know what’s going to happen? So it was kind of the same mindset. And he was anticipating what was to come, so he was dreading it a little bit, but he knew that this is as bad as it is going to get, and I can get through to the other side” (124:6).  
|                                                                      | • Nurse: Patient had anxiety surrounding receiving Demerol because of his past experience with the PRN medication. “He was very worried about getting Demerol for rigors because he said the last time he had urinated in a trash can or he had gotten confused and they related it to the Demerol. So he definitely did not want Demerol. That was his big request” (124:9).  
|                                                                      | • Care Partner: Another trigger to the anxiety was the discrepancies in provider communication. “I mean one person is calling it immunotherapy, one person is calling it chemotherapy, one person is calling it IL-2, one person doesn’t know how to pronounce it. I mean, it’s just we got very confused through part of the process. Are these chemo treatments, are these not chemo treatments? We’re not going down a path of chemo specially. We already know that chemo does not help with kidney cancer, so why does one person call it chemo, one person calls it immunotherapy, one person calls it immune booster therapy, just everybody get on the same page so we know what’s going on. But that’s my only thing from the doctors and the PAs and the nurses, and they all are doing this program so let’s get on the same verbiage with the program” (124:8).  
| Increased Sleep                                                      | • Nurse: As early as dose 2, the nurse noted that the patient looked tired (126:41).  
|                                                                      | • Care Partner: Increased sleep maybe related to PRN Morphine for his rigors (126:26).  
|                                                                      | • Care Partner: Increased sleep around dose 3 (126:29).  
|                                                                      | • Care Partner: Treatment ended after dose 5. Severe fatigue after bad episodes of rigors.  
| Cycle 3                                                              | • Nurse: Irritability. (Irritability was not present in first two treatment cycles) (125:3).  
| Decreased Sleep                                                     | • Care Partner: Initially decreased sleep starting at dose 1 because of severe rigors (126:33).  
| Increased Sleep                                                     | • Care Partner: By dose 3, he was sleeping most of the day (126:34).  
| Cycle 4                                                              | • Patient: Restless sleep. “Started between treatments. I don’t know what it was but I’d lay back and think that I was asleep and then I’d wake up a few minutes later and it’d be five minutes. It went on and on and on for five and ten minute increments. So I never did get any restful sleep yesterday at all” (126:22).  
| Decreased Sleep                                                     | • Care Partner: Irritability. “He barks at me if I ask him if he wants anything” (125:1).
| Increased Sleep | • Care Partner: Increased but restless sleep (126:35).
• Care Partner: Sleeping a lot by dose 3 with more severe symptoms (126:36). |

5.5.3.3 Case Study: Exemplar 2

The index participant was a white male in his 60’s with his wife as his care partner. The patient received seven doses during cycle 1, five doses during cycle 2, seven doses during cycle 3, and four doses during cycle 4 of treatment. See Figure 28 for pre- and post-treatment depressive symptom scores. The patient self-identified high depressive symptom scores at post-treatment of cycle 1 and cycle 2 on the PROMIS-8B. While these self-reported symptoms improved for cycle 3 and cycle 4, depressive symptoms remained in the “mild to moderate” depressive symptom range at post-treatment for all time points as reflected on the IDS-C. Similar to exemplar 1, scores on the IDS-C suggest that while the index participant for exemplar 2 did not experience residual depressive symptoms across treatment hospitalizations, he did experience transient depressive symptoms within each treatment hospitalization.
While there were fluctuations in sleep disturbance symptoms, sleep disturbance worsened by the end of each treatment cycle but was by far the worst at the end of cycle 4. Sleep disturbance symptoms returned to baseline prior to the start of each subsequent treatment cycle.
See Figure 30 for pre- and post-treatment anxiety scores. The patient was able to identify severe anxiety in himself, as reflected on the self-report PROMIS-8A. This was congruent with the clinician-rated HAM-A, which also showed that anxiety symptoms worsened across each treatment cycle. According to the PROMIS-8A, anxiety symptoms were by far the worst at the end of treatment cycle 1.
Figure 20: Total anxiety symptom scores at pre- and post-treatment for each treatment hospitalization

See Table 19 for qualitative reports of affective and sleep disturbance symptom change. Beginning at cycle 1 of treatment, anticipatory anxiety was problematic for this patient. Initially he had anxiety related to the unknown of what would happen during treatment. Later, after having a rigor episode that was very difficult to manage, the patient would become anxious before each dose, watching the clock for the rigors to set in. Ativan helped manage his anxiety around the timing of his rigors. He was also irritable and on edge, making requests, but unable to attain comfort.

The patient reported that his anxiety came back for cycle 2 because the first cycle was so bad for him. He was a little calmer because he knew what to expect, but anxiety
was still very much present. His anxiety symptoms heightened when his PICC line was delayed and his first dose of treatment was delayed. Clock-watching continued. His wife believed his anticipatory anxiety made his rigors worse, as he was just waiting for the symptoms to occur. He also had anxiety surrounding the possibility that his only working kidney would be destroyed. He felt a sense of relief when he knew that treatment had ended for the cycle. The patient had increased irritability towards the end of treatment in cycle 2 and was unable to get comfortable.

During cycle 3, his anxiety continued and became particularly bad during dose 6 when he felt like he could not get a good breath. Initially he experienced decreased/restless sleep around the timing of his rigors, but overall increased sleep started at dose 2. During cycle 4, anticipatory anxiety continued along with irritability and indecisiveness. His sleep decreased significantly and he experienced interruptions.

Table 19: Qualitative reports of affective and sleep disturbance symptom change from exemplar 2

<table>
<thead>
<tr>
<th>Treatment Cycle</th>
<th>Symptom</th>
<th>Quote/Evidence</th>
</tr>
</thead>
</table>
| Cycle 1         | Anxiety | • Both he and his care partner identified anticipatory anxiety in the patient before each dose of IL-2. The patient described his anticipatory anxiety as, “At first I think (the anxiety related to) the unknown of what was coming. And then after I had been through the duration I was anxious because I had that first really bad ah rigor. So I was most anxious every time that came around. And I just played the clock saying, ‘Okay I had the infusion at 10, it should be here at 2. I’m gonna be ready for it at 1.’ You know and be ready to go with morphine and- and the heat blankets because the one-the third episode I fell asleep and I slept calmly. I was awake and already in the rigors full stage and that was a mistake I said I’d never make again. I mean I set the alarm clock here and my wife set her alarm clock and she was- she’s a gem” (124:37).
• The care partner identified that her husband would get very anxious if he had |
a really bad experience with his rigors. If he had an okay experience during the dose, then he would shift his focus on to making it through the next infusion (124:47).
• Ativan helped decrease his anxiety around the timing of his rigors (124:44).

Irritability

• The patient described to his wife that he was feeling very antsy and on edge (124:44). According to his care partner, “He was kind of getting to that point and-and so um, he went on and had the infusion at um at noon and um, and then about 5:00 he just started getting really irritable and anxious again. And finally he says, ‘Can I maybe get that Ativan again?’ And so (the nurse) gave him the Ativan and that seemed to help but he was still just like kind of really agitated and that was the worst time it was like- he had on like you know golf socks like ankle socks, ‘I need you to get my socks off.’ I said, ‘Alright.’ So I took his socks off and then it was like, ‘I need to go to the bathroom. Put my socks back on so I can go to the bathroom.’ I said, ‘Okay’ so we put his socks back on and he went to the bathroom. Then he goes, ‘I need to go for a walk’” (124:45).
• With this increased anxiety and irritability, his wife remembers watching his heart rate become elevated on the monitor, and tried to calm him down and help him sleep (124:46).

Decreased Sleep

• Patient reported to his wife that he was having difficulty sleeping (dose 2) related to interruptions with the nurses and alarms (126:58).

Cycle 2

Anxiety

• The patient had anxiety coming back for the second cycle of IL-2 treatment having known how bad the first cycle of treatment was for him (124:40/124:41).
• The care partner said, “Before returning for this cycle, (name) said he was more confident this time because he ‘knows what to expect.’ But I can tell he’s got some mild anxiety. Since we got to the room he’s almost ‘over-compensating’ with his humor, pacing, etc” (124:70).
• When he got checked into the hospital for cycle 2 and things didn’t go according to plan (i.e. his PICC line insertion was delayed and therefore his for dose of treatment was delayed), he got antsy and anxious. He felt prepared and in a good state of mind but this threw him off (124:56).
• His wife described his experience with anticipatory anxiety as almost causing or worsening his anxiety. She said that he stated, “I’m just so- I already feel like I’ve got the chills. This is just not a good sign that this is happening before I ever start the infusion.’ And so of course that I think gave him a little more anxiety to deal with. And um, and he did say that last time we were here he said- he says, ‘I know I’m such a clock-watcher. It’s like I watch the clock and wait for the next thing to happen’” (124:61).
• His wife stated, “But he you know- at one point I told him I said, ‘I swear I’m just gonna get a towel and hang it over it. If the nurses didn’t need it I would do that.’ But um, he goes, ‘No, don’t- I need to see the clock. I need-.’ I said, ‘Okay, okay’” (124:62).
• As soon as treatment ended for the cycle, the patient reported experiencing a sense of relief and that his anxiety left (124:39).
• He did find that distractions were helpful, for example when the student PA came in to examine him, which took a lot longer than for the PA to examine him, but it was a good distraction (124:64).
• The care partner also described the patient as tearful and emotionally labile.
(123:7). The wife described her husband’s struggle with treatment as, “He goes, ‘I’m just so tired. I’m so exhausted. I’m just having such a hard time staying focused.’ You know and um, and then he said- he goes, ‘You know I- I just don’t know if I can do this again.’ And I said, ‘Well like the rigors?’ And he said, ‘Yeah but more the fact that I’m spinning and I can’t- I can’t stay focused and I can’t-.’ And I said, ‘Well we’ll just have to see how it goes you know what I mean?’ He said, ‘And I just I’m feeling so anxious’” (124:58).

- The patient was also very concerned and worried about destroying his only good/working kidney and was very concerned about his decreased urine output during treatment (124:66).

<table>
<thead>
<tr>
<th>Irritability</th>
<th>Towards the end of treatment, his wife notices increased irritability and an inability to get comfortable (125:14).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased Sleep</td>
<td>The care partner described that last time his symptoms were bad and then he would calm down and be able to sleep a little before his next dose. During this cycle, his symptoms never fully resolved and were particularly bad during the night, so her husband really did not sleep during treatment (126:78).</td>
</tr>
<tr>
<td></td>
<td>Very restless sleep according to the nurse (126:79).</td>
</tr>
<tr>
<td>Cycle 3 Anxiety</td>
<td>The care partner described her husband’s continual anticipatory anxiety as, “I did say I was going down to get some lunch and he says, ‘just make sure you’re back here by’ whatever time cause he says, ‘You know that’s when- cause that’s when the rigors will start.’ And I said, ‘Oh my gosh! I swear if you nurse’s didn’t need that clock I would take it down.’ And he goes, ‘No, I’m living by that clock.’ I said, ‘I know! Sometimes I think you work yourself into that, it’s anticipatory for you. I really think you just sometimes you work yourself up for it.’ And he goes, ‘No I just I know when it’s coming.’ And so as it gets closer and that’s kind of more so as little long- you know the first time he was a little bit anxious about it. But then with the second one when he didn’t even have to have any Demerol and he didn’t have any rigors it was like, ‘Huh, okay’ you know? And- and so I saw less of it but then as we started getting to number six and you know and number seven it was a lot more of the anxiety of what was to come” (124:74).</td>
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<td>Around dose 6, the care partner reported severe anxiety, stating, “By 8pm he started feeling like he couldn’t get a good, deep breath and got really anxious. When nurse said his O₂ saturation was 98% he relaxed a little. He wanted his laptop, but then said, ‘Never mind, I can’t focus on it.’ Asked for a book and then said he couldn’t concentrate enough to read. He started wheezing and requested breathing tx. About 9:10p*, rigors started. I was down in the cafeteria and the response with Demerol was delayed when I got back to room at 9:30p. He was having terrible rigors, the respiratory therapist was starting his tx. The Demerol was given about 9:40p. He had violent rigors and then they added another drug at 10:30p that finally slowed the rigors. He was stuttering and mumbling until almost 11:15p. He got a 2nd breathing tx and finally fell asleep. He mumbled in his sleep and was up and down going to bathroom until 1 AM. *According to nursing assistant” (126:72).</td>
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- Patient experienced restless sleep and was tired with his rigors (dose 3) (126:70).

- Increased sleep started at dose 2.
• Similar to previous treatment cycles, the patient came in with anticipatory anxiety. “About two days before we come- he starts getting a little snippy and getting you know and that kind of thing and- and then he’ll start getting- as we get in the car to drive up here he starts getting really quiet. And I can tell his mind is just spinning you know? And I’ll say, ‘What you thinking? What are you thinking about?’ He goes, ‘A million things and nothing.’ You know that’s his thing. (P laughs) And so- so you know he just all of this is- is running through his mind. And so- and then you know and then we get here and he’s like almost overcompensating by you know with his humor and his- and his bravado and that kind of thing. And then when it comes down to it he gets the first infusion and then he’ll be just lying there quietly and I’ll say, ‘What are you thinking about?’ He goes, ‘I just always get anxious thinking about those rigors coming.’ So you know it’s just- it’s just the routine and it- and that has been consistent since day one” (124:79).

Irritability

• During the rigors he gets very irritable and indecisive about what he wants (124:80/125:19)

While not reflected quantitatively on the HAM-A or PROMIS-8A standardized measures, qualitative reports from the patient and care partner suggest that the index participant experienced residual anxiety, and his anxiety level prior to his hospital admission for each subsequent treatment cycle was related to the severity of his previous symptom experience.

5.5.3.4 Case Study Exemplar 3

The index participant was a white male in his 50’s who had his wife as his care partner. The patient received eight doses during cycle 1, four doses during cycle 2, five doses during cycle 3, and four doses during cycle 4 of treatment. See Figure 31 for pre- and post-treatment depressive symptom scores. Clinician-rated depressive symptom scores increased at the post-treatment time point for all treatment cycles, but depressive symptoms were by far the worst after cycle 2. Self-report depressive symptom scores
were not congruent with clinician-rated scores. Similar to the previous two exemplars, scores on the IDS-C suggest that while the index participant for exemplar 3 did not experience residual depressive symptoms across treatment hospitalizations, he did experience transient depressive symptoms within each treatment hospitalization.

![Exemplar 3: Depressive Symptom Total Scores](image)

**Figure 21**: Total depressive symptom scores at pre- and post-treatment for each treatment hospitalization

See Figure 32 for pre- and post-treatment sleep disturbance symptom scores. Sleep disturbance scores increased across the first three treatment cycles but remained stable. Sleep disturbance was minimal during cycle 4 of treatment.
Figure 22: Total sleep disturbance symptom scores at pre- and post-treatment for each treatment hospitalization

Exemplar 3: IDS-C Sleep Subscale Scores

See Figure 33 for pre- and post-treatment anxiety scores. The patient self-identified anxiety during his post-treatment interview(s) but his rating on the self-report measure suggested that his anxiety levels were unchanged within the treatment cycle. Clinician-rated anxiety scores suggest that anxiety was higher at post-treatment in comparison to pre-treatment time points.
See Table 20 for qualitative reports of affective and sleep disturbance symptom change. During cycle 1, the patient experienced anticipatory anxiety surrounding pain and rigors and kept repeating that he was dying. Irritability increased with his anxiety. The patient and his care partner agreed that his sleep decreased starting at dose 4. He was restless and unable to get comfortable. During cycle 2, he was anxious prior to his hospital admission because of conversations with doctors. His anxiety worsened after each IL-2 dose, and he had a huge fear of choking on his vomit. He was very irritable and became very depressed, according to his care partner. He had one hallucination where he thought his nurse was in the room with a coffee pot, which was around the time when he received Ativan. The patient oscillated between increased and decreased sleep. During cycle 3, although he still had anxiety, he had much less than what he
experienced during his previous treatment cycles. The patient attributed this decrease in anxiety to knowing what to expect during treatment, and he was determined to “do better.” He was still irritable but much less so than during cycle 1 and cycle 2. He reported no sleep disturbance symptoms during cycle 3. Anxiety started the week before he was admitted for cycle 4, and he became very irritable. He reported decreased and restless sleep for the duration of treatment cycle 4.

Table 20: Qualitative reports of affective and sleep disturbance symptom change from exemplar 3

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<tr>
<th>Treatment Cycle</th>
<th>Symptom</th>
<th>Quote/Evidence</th>
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<tbody>
<tr>
<td>Cycle 1</td>
<td>Anxiety</td>
<td>• The patient had anticipatory anxiety worried about pain and rigors (124:88/124:89). • Patient kept stating, “I’m dying, I’m dying” worrying about the treatment and the severity of his symptoms (124:93).</td>
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<td>Irritability</td>
<td>• The care partner noted that he was irritable and an increase in anxiety in between doses uncertain if his body could physically handle the treatment (125:37). • He became very argumentative, refusing to take his shorts off that were saturated in urine (125:35) and arguing about what dose number he was on (125:36).</td>
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<td>Cycle 1</td>
<td>Decreased Sleep</td>
<td>• The patient experienced decreased sleep as treatment continued (126:112). The patient noted that his sleep was very restless, “I would still be in bed but I would be- I would be awake. I would be flipping back and forth to either side of the bed. Sometimes I’d even flip to the end- end of the bed. It was like I could never get comfortable cause I was kind of always in pain” (126:107). • His care partner stated that at dose 4, even though he was exhausted, he was sleeping less. She said, “Tired from shaking. Not able to sleep due to shaking several hours—did not want morphine, thought it might make him sick. Was given Ativan 1st to stem off nausea due to morphine but still refused a half dose. Anxiety increased when shaking began. Was not able to sleep but a couple hours. Lost track of what day it is and treatment dose number. Shaking began not long after dose was given. Harder than had been for past doses. Nausea even without the morphine. Cold. Headache” (126:115).</td>
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<td>Increased Sleep</td>
<td>• By dose 5, he shifted towards increased sleep (126:116) and became difficult to wake up and arouse by dose 7 (126:117).</td>
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### Anxiety

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<th>Cycle 2</th>
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<td>• The patient described his severe anxiety as, &quot;Yeah it was more than a little, the anxiety all started because- well originally the doctor’s when I first came here they told me that this was gonna be really bad. And- and you know the first treatment and just kept over and over telling me how toxic this was and it’s just gonna be bad. And I thought- my first thought was, 'Well you’ve just had a bunch of wusses here who you know- I’m gonna get all the doses in.' And then I realized they were correct. So then after we get done with those first doses I’m told, 'Yeah when you come back for the second doses they’re gonna be even worse. You’re gonna have the response right away.' So yeah that just made me fearful and anxious about what was gonna happen when they gave me that dose&quot; (124:90).</td>
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<td>• The care partner confirmed that her husband had anxiety before they had even arrived at the hospital (124:95).</td>
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<td>• The patient also stated that his anxiety got worse after each IL-2 dose (124:90).</td>
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<td>• Part of his fears and anxiety stemmed from the fear of choking on his vomit and his care partner stated that he became very anxious around doses 3 and 4 where he was vomiting; Ativan was given to help with nausea and anxiety (124:96).</td>
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<td>• His care partner described, &quot;After the third and when he said he would do the fourth he started getting really agitated. And um, he said he felt like he was crawling out of his skin and he you know- and so finally the nurse says, 'Do you want some Ativan?' And he said, 'Yes, give it to me.' Just because he knew that was the anxiety about the vomiting. He tried to go to the bathroom and then said, 'I just can’t do it. I can’t focus enough to use the bathroom.' And I said, ‘Do you need help?’ And he was, 'No, no, just leave me alone. Let me think about it.' And he just laid there. So he didn’t even sit up and try or anything. He just you know sit you know fall right back asleep” (124:97).</td>
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### Irritability

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<td>• His care partner noted that he became irritable, anxious and depressed on the day of his admission saying that he was going to cancel and reschedule the treatment, yelling (123:9).</td>
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<td>• The patient also was aware of his irritability and unwillingness to be cordial towards his wife during treatment (125:31).</td>
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### Depressive Symptoms

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<td>• She described him as not joking, being very matter of fact, and having a flat affect (123:22).</td>
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<td>• As treatment continued, “He got just more of that withdrawn, flat, uhm but I honestly I couldn’t put it all on if it was from the IL-2 or if it was from his anxiety related to, uhm, like a fight or flight almost. Like he was doing all he could do to answer the question I asked him” (123:23). He would wake up moaning, saying, “(I’m) dying” (123:17).</td>
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### Hallucinations
- The patient recalled one episode of hallucinations as, “But I was just sitting in bed and I thought I saw the nurse come in with ah a coffee pot and was gonna hook it up and make us coffee. And I told (my wife), I said, ‘The nurse is here. She’s got coffee- got a coffee pot and gonna make us coffee.’ And (my wife) looked at me and she says, ‘What are you talking about? There’s nobody here.’ And then of course I look and I was like, ‘Oh you’re right.’ But I could have swore while I was looking straight ahead that I was seeing a nurse in here with a coffee pot” (123:12). His care partner wasn’t sure if this episode was related to him having just received Ativan (123:16).

### Decreased Sleep
- The patient described his sleep as terrible and saying that he “would go sometimes almost twenty-four hours with no sleep” and, “The medication gets you completely off of your regular sleep schedule. And then they- I was given stuff to try and knock me out so I wouldn’t you know have all this vomiting, which that did not work either. Um, but those things, when they gave me those medications it might put me out for an hour or two, maybe three and then I’d wake back up and I just did not get near the amount of sleep that I would normally get at home. Plus you know the uncomfortability of being in this room, being hot, itching, things just kept me up the whole time” (126:108).
- The care partner noted decreased sleep surrounding doses 1 and 3 related to his nausea and vomiting (126:133/126:135).

### Increased Sleep
- The care partner also noticed increased sleep surrounding doses 2 and 4, with increased dreaming during dose 4 (126:124/126:123).

### Cycle 3
#### Anxiety
- Coming back for Cycle 3, he didn’t have as much anxiety and fear surrounding his nausea as he did in previous cycles (124:101).
- His wife also said that while he had anxiety when he was admitted, it was nothing compared to Cycle 2. She said, “Um he was anxious before we got here, but I don’t think he was anxious before each dose. Not like- I don’t think it was like the second time we were here he was really anxious in between each dose and was really dreading the next dose. Um and kept saying, ‘I’m gonna die, I’m gonna die. I’m dying’ or whatever. And that really didn’t- he just kept saying, ‘I feel like I’m dying,’ I was like, ‘You’re not.’ And he goes, ‘I know’” (124:102).
- His wife said that coming back he knew what to expect and he was determined so overall he seemed to do better (124:104). Knowledge helped stabilize his anxiety (124:101).

#### Irritability
- He was argumentative like last time but it wasn’t horrible according to his care partner (125:47).
- He was also fidgety and said he was “bouncing to keep the rigors away” (125:46).

### Cycle 4
#### Anxiety; Irritability
- According to the care partner, his anxiety started the week before treatment (124:106).
- He would show his anxiety by, “Being irritable. Um he’ll do like as soon as he gets the dose he sits on the side of the bed and rocks a little bit. Um and name-name would ask him, ‘Did you need something?’ ‘No.’ And he would just sit and kind of do this. And he would say his back hurt and stuff like that- that you could tell he was anxious” (124:105).
- Continued to say he was dying (123:10/125:54). Irritability and decreased
Qualitative reports suggest that this index participant had residual anxiety symptoms surrounding incongruent language used by medical personnel; while one person would call IL-2 an immunotherapy, another healthcare professional would refer to the treatment as a chemotherapy agent, and the terminology used to label the drug was often incorrect. The patient at one point stated he was told that chemotherapy was an ineffective treatment for his cancer type; therefore, hearing IL-2 classified as chemotherapy created confusion and provoked anxiety. Symptoms of anxiety were present at the time of each hospital admission, suggesting that anxiety levels did not return to baseline at the end of each hospitalization. In addition to anxiety and depressive symptoms, this index participant also reported sleep disturbances.

**Decreased Sleep**

- The patient experienced minimal and interrupted sleep. He said, “The vast majority of the time I could not sleep. I would drift off for a little bit here and there. And when they’d give me the Morphine and the Ativan I would sleep for a few hours. And then I’d come right out of it and be up and irritated the rest of the time till I got another dose” (125:34).
- His care partner also described his sleep as restless, “Um he sleeps in between-like he’ll sleep in between like when the nausea abates he- he kind of dozes off. And then when he gets the chills- once the chills are over he’ll nod off and that could be due to medication. Ah now I will say that- so he’s nodding on and off kind of a lot, it’s not really restful sleep. Um but the second dose he slept pretty much through the night unless I woke him up. And there was a few times they’d bring the pills in and say, ‘just make sure he takes that.’ And so I just wake him up and make him take pills and he’d go right back to sleep. So um but last night he slept most of the night through except for getting up to go to the bathroom” (126:127).
5.5.4 A Posteriori Definitions

Qualitative reports of affective and sleep disturbance symptom change over the course of treatment gave the study team a new understanding of each a priori symptom definition, and the team then formed a posteriori definition for each code (McKenna et al., 2014). Each a priori code definition from the original codebook was then compared to the new a posteriori code definition, derived from data analysis. For example, there was no a priori definition for anticipatory anxiety; however, anticipatory anxiety was highly prevalent and the team defined it as, “Clock-watching that can be related to the severity of symptoms.” A nurse described, “There’s definitely anticipatory [anxiety] for the rigors. He was working himself up waiting for the rigors” (124:33). She added, “He definitively was sitting there watching—watching the clock waiting for [the rigors] to hit him” (124:34). Some patients were even incapacitated by their anxiety, screaming for help. For example, a wife described her husband’s severe anxiety exacerbated by the timing of his rigors,

He was saying, ‘Help me. Help me’ he was just- his teeth were clenched. His fists were clenched and he just couldn’t- he just couldn’t stop. And that went on for about forty-five minutes. It was pretty scary. You could see just his face was just frozen. And- and he had his teeth exposed and just- I felt really bad for him” (124:125).

Decreased anxiety was re-defined as “Anxiety that ebbs and flows based on time until/after treatment and decreases as the patient moves away from the last treatment.”
Proactive medication management, support from friends/family, and increased distractions decreased anxiety. A care partner witnessed a decrease in anticipatory anxiety if/when the patient learned which PRN medications to ask for to manage his symptoms. By dose 4, he figured out that if his toes got “cool,” he needed to ask for something to manage his rigors/chills. The care partner believed that if her husband knew what to expect and what was coming, he would be less anxious.

**General anxiety** was re-defined as, “The inability for the patient to explain what was contributing to anxiety and the inability to get comfortable.” General anxiety surrounded factors such as waiting for the follow-up scan to determine if treatment was effective, the unknown, receiving IL-2 for the first time, and variability in provider communication regarding the name of treatment and the target number of doses to complete.

**Depression** was re-defined as, “Flat, withdrawn, wanting to be ‘left alone,’ tearful, and emotionally labile.” One wife said that as treatment continued, her husband exhibited depressive symptoms: “He was worn out and wasn’t interested in talking or having conversations and just wanted to be left alone” (123:5/123:6).

**Irritability and agitation** were merged, and re-defined as, “Indecisiveness and feelings of being out of control, occurring with anxiety, exhaustion, and worsening symptoms.” These symptoms increased with lack of sleep, rigoring, confusion and
short-term memory alterations. A care partner described irritability,

If you asked him [a question], he got a little irritable and said, ‘Don’t talk’ and [would] bring his hands out of the covers, ‘Don’t talk.’ Then when I got in he said, ‘I have to pee.’ So you know I helped him stand up but he was grabbing for the basin. And I said, ‘Are you sick?’ ‘No, I have to pee.’ And I said, ‘Well I have to get the urinal, not the basin.’ (125:6)

Another care partner described her husband as frustrated and unable to get comfortable. These changes occurred around dose 4:

He was very fidgety. He was, he’d raise the bed, he’d lower the bed. He’d…up and down and he was like, and I just said, I said, ‘Why don’t you just roll over. Let me just rub your back.’ ‘I’m okay, I’m okay.’ You know? ‘I just can’t get comfortable.’ (125:58)

Hallucinations and vivid dreams were merged and re-defined as, “Talking during sleep or seeing things that were not there.” Oftentimes it was difficult for the patient to differentiate between hallucinations and vivid dreams. These alterations would also occur around the timing of rigors or when a PRN medication was administered. One patient described an episode where he believed the nurse was in his room asking him questions, but when he opened his eyes, he realized she wasn’t actually present. He was unable to discern if he was having a vivid dream or a hallucination. Another patient described his hallucination,

I would have my eyes closed and I’d be at work—where I used to work on the railroad and I’d see people I knew at the railroad. But I’d been doing stuff that is impossible to do at the railroad. Like I would be lying there and I’d pick up the rail with one hand which you can’t do, it’s too heavy. And I’d pick it up and help load the rail on the rail train. So I’d do
like that and then all of a sudden like I was picking up the railing and putting a couple of rails together and I opened my eyes and would be reaching for something-and then I’d be looking around and say, ‘Hey I’m not here.’ (123:20)

Under the sleep disturbance construct, **decreased sleep** was re-defined as, “Sleep typically decreasing initially towards the beginning of the treatment cycle.” **Restless sleep** was determined to be a subcategory of decreased sleep and was defined as “Restless or interrupted sleep, which is sometimes related to anticipatory anxiety.” **Increased sleep** was re-defined as, “An inability to stay awake.” Increased sleep occurred with increased fatigue. Sleep typically increased towards the end of the treatment cycle. One patient reported experiencing increased sleep towards the end of treatment where the longest she was awake was for, “About an hour” in a 24-hour period.

**5.6 Discussion**

Many of the affective and sleep disturbance symptoms qualitatively reported by the patient receiving IL-2, their care partner, their primary nurse and/or nurses were not captured by the self-report standardized measures, but were relatively captured by the clinician-rated measures. This is likely one of the reasons why affective and sleep disturbance symptoms often go unidentified and unmanaged in the IL-2 patient population. Because quantitative measures did not capture the holistic symptom experience, the qualitative component of this study was crucial to the understanding of
the symptom trajectory and symptom experience. Qualitative data analysis allowed the study team to develop new affective and sleep disturbance symptom definitions as well as modify previous symptom definitions to provide a more accurate understanding of what the symptom trajectory looked like, how symptoms presented, and how these symptoms changed over the treatment hospitalizations. Many of these symptoms would have been overlooked and gone unidentified if the index participant was evaluated with standardized measures alone, particularly those with limited symptom content. This case study highlighted the importance of qualitative reports to not only identify affective and sleep disturbance symptoms, but also to understand their frequency, duration, severity, and how they change over the treatment trajectory. This is essential for the development of targeted and effective therapeutic interventions in this population.

There seems to be a relationship between sleep disturbance symptoms, anxiety, and depression. As sleep disturbance symptoms increase, clinician-rated depressive symptoms and clinician-rated anxiety symptoms also worsened. In several cases, depressive symptoms were found to have a cumulative effect. For example, as shown in exemplar 1, depressive symptoms were correlated to the number of IL-2 doses the patient received. In cycle 1, the patient received seven IL-2 doses in comparison to cycle 4 where he only received four doses of IL-2, and his depressive symptom score was the highest (i.e. most severe) at the post-treatment time point for cycle 1. Because sleep
disturbance is a subscale on the IDS-C, increased sleep disturbance scores contributed to the increased total IDS-C scores. Of similar note, sleep disturbance is a major depressive disorder symptom domain, and sleep disturbance albeit insomnia or hypersomnia, plays a role in the depressive symptom experience. While the IDS-C Sleep Disturbance subscale provided a numeric value depicting the severity of sleep disturbance symptoms, this number does not give clinicians or researchers an understanding of what sleep disturbance symptoms look like. For example, these scores do not indicate whether the patient scored poorly because they were experiencing insomnia, hypersomnia, or both during the treatment cycle. To identify this information, the clinician would need to examine the individual sleep disturbance items, which isolate early, middle, and delayed insomnia, and hypersomnia. Importantly, this is where qualitative reports are beneficial and essential in capturing these unique data to inform the care partner and healthcare team in order to deliver targeted interventions aimed at managing symptoms.

There tended to be incongruence between symptoms captured on the self-report and clinician-rated standardized measures. Perhaps this was because the self-report measures were in short form, and therefore were too abbreviated to truly evaluate the symptoms this patient population experienced. Of importance, as there are multiple versions of the PROMIS depression and anxiety measures that range in number of symptom items captured (e.g., 4-item, 7-item), this study employed the versions with the
maximum item content (eight items each). While some patients were in tune with their symptom experiences, others heavily relied heavily on their care partners to fill in the gaps as to what they experienced and when, which substantiates the value and importance of the care partner residing at the bedside during aggressive treatment. Importantly, while the IDS-C detected changes in depressive symptoms, the PROMIS-8B was not sensitive to depressive symptom change. The IDS-C evaluated sleep symptoms, whereas the PROMIS-8B did not, which may be one of the many reasons why the PROMIS-8B was too abridged and was not appropriate for detecting depressive symptom change within- and across-treatment hospitalizations. Similarly, anxiety symptom trends looked vastly different on the clinician-rated HAM-A measure in comparison to the self-report short-form PROMIS-8A measure across treatment hospitalizations. Even though anxiety was a recurrent theme in nearly all index participants, these patients had difficulty identifying their anxiety symptom alterations on the self-report PROMIS-8A, although they verbalized severe anxiety symptoms during their post-treatment interviews. These qualitative reports of anxiety by the index participants were supported by qualitative reports from care partners, nurses, and researchers.

Two main symptom areas researchers can focus intervention development efforts on are the management and prevention of sleep disturbance symptoms and
anticipatory anxiety. These symptoms often exacerbate the overall symptom experience. The concept of “anticipatory anxiety” has been described surrounding nausea events in adolescent cancer populations receiving chemotherapy. Adolescents who experienced higher anxiety symptoms also reported that they experienced more severe nausea compared to those who reported lower levels of anxiety (Ameringer, Elswick, Shockey, & Dillon, 2013). This may be similar to the anticipatory anxiety surrounding the timing of rigors in patients receiving IL-2 where patients who experience more severe anxiety also experience more severe rigor episodes. Therefore, anxiety may heighten and worsen the symptom experience, where previous negative symptom experiences and anticipatory anxiety increased the anxiety experience, while knowledge about the treatment and symptoms can decreased the anxiety experience.

Interventions such as relaxation and hypnosis, and alternative medicine approaches including acupuncture and herbal supplements have been recommended for anticipatory nausea, as they aim to decrease these learned behaviors, which may be resistant to pharmacologic intervention (Kamen et al., 2014). Chesla (2010) found care partner interventions particularly beneficial in reducing affective symptoms in patients with chronic illnesses.

Sleep symptoms have yet to be investigated in patients receiving IL-2. Research conducted with other cancer cohorts highlighted that sleep disturbance symptoms
continue to exist after cancer patients end treatment, and these sleep disturbance symptoms can have significant consequences on the individual’s relationships, health, cognitive function, and other affective symptoms (i.e. irritability, depression, anxiety) (Fleming, Gillespie, & Espie, 2010). Sleep disturbance symptoms can have a major impact on quality of life, particularly when altered sleep becomes a chronic problem and the patient is unable to return back to his or her pre-treatment sleep patterns when treatment has ended.

Future interventions can target education for the patient and care partner prior to and during hospital admission for IL-2 treatment. Education about the illness trajectory and what to expect during and after treatment has been shown to help care partners and patients set realistic shared expectations, increase coping mechanism, and decrease feelings of powerlessness (Guo et al., 2013; Northouse et al., 2010; Williams, 2007). Although most research focuses on patient interventions, care partner interventions have been found to not only help the care partner but also the patient in decreasing negative outcomes such as depression, anxiety, and distress (Guo et al., 2013).

Interventions can also target the healthcare team, such as education on proper terminology, and assuring the healthcare team is presenting consistent information to patients and their care partners. These simple changes can reduce anxiety, confusion, and stress in patients and their families.
Understanding the trajectory of affective and sleep disturbance symptoms allows providers to identify critical time points when symptoms present and their trajectory of change during and after treatment. Points of trajectory change are potential time points where future interventions could be introduced to manage IL-2-induced symptoms. Interventions directed at the patient can address transient or residual symptoms, and these interventions can include pharmacological or non-pharmacological interventions, which can be initiated by either the provider, care partner, or patient. Equally as important, interventions should also target the patient/care partner dyad with the goal to build a long-lasting, strong relationship while reducing the negative outcomes that care partners frequently experience but are oftentimes overlooked.
6. Conclusion

Cognitive, affective, and sleep disturbance symptoms impact patients receiving aggressive treatment for life-limiting chronic illnesses, such as cancer (Chen, Miaskowski, Liu, & Chen, 2012; Joly et al., 2015; Mielcarek et al., 2016; Reilly et al., 2013). To better understand the presentation of these symptoms over the course of treatment, this study examined the symptom experience of patients receiving Interleukin-2 (IL-2) therapy for metastatic renal cell carcinoma (MRCC) through a case study approach. This dissertation was the first step in my program of research, and the methodologies discussed in this dissertation will be applied to a broader context in prospective scientific investigations that seek to understand the cognitive, affective, and sleep disturbance symptoms patients undergoing aggressive treatment for life-limiting chronic illnesses experience. Findings from this dissertation can better equip care partners and providers to manage the immunotherapy-related cognitive, affective, and sleep disturbance symptoms that present in MRCC patients receiving IL-2 therapy as well as similar symptoms in other populations undergoing aggressive medical treatment. Additionally, the methodology used to understand the symptom trajectory of patients receiving high-dose IL-2 can be applied to other populations receiving treatments with dose-limiting toxicities.

Each chapter was associated with a specific aim, as follows:
• Aim 1 (Chapter 1): To position the problem in the larger context of symptom science.

• Aim 2 (Chapter 2): Conduct a systematic integrative review of the literature on IL-2-induced cognitive and affective symptoms.

• Aim 3 (Chapter 3): Investigate one case (patient receiving IL-2, care partner, and primary nurse) during one hospitalization for IL-2 therapy to evaluate the feasibility of the proposed research methods to generate knowledge surrounding the IL-2 symptom trajectory.

• Aim 4 (Chapter 4): Describe the trajectory of IL-2-induced cognitive symptoms in ten patients receiving IL-2 therapy using a mixed-method case study approach.

• Aim 5 (Chapter 5): Describe the trajectory of IL-2-induced affective and sleep disturbance symptoms in ten patients receiving IL-2 therapy using a mixed-method, case study approach.

6.1 Summary of Findings

6.1.1 Chapter 2: Cognitive and Affective Symptoms Experienced by Cancer Patients Receiving High-Dose Intravenous Interleukin-2 Therapy: An Integrative Literature Review

The study team began with a literature review to understand the prevalence and level of severity of IL-2-induced cognitive and affective symptoms and synthesized findings to determine areas for future research to address the challenges that patients,
care partners, and healthcare providers face as a result of these symptoms (Mann et al., 2015). This literature review described the patient experience when undergoing high-dose IL-2 and the pathophysiology leading to these changes.

There is a substantial gap in the literature when it comes to identifying cognitive and affective alterations across the course of IL-2 treatment. While patients undergoing treatment with IL-2 and their care partners have reported cognitive and affective symptoms to be the most alarming and difficult symptoms to tolerate and manage, these symptoms were often unidentified in published literature, and were primarily identified through modalities such as online patient forums. Many patients agreed that these symptoms were inadequately screened, and patients were uninformed about these potential changes (Ejneary, 2011).

Furthermore, there was a lack of standardization in the assessment, reporting, and management of affective symptoms. The authors were unable to locate studies that described the trajectory of cognitive symptoms. To date, no published study has described the degree of neurotoxicity in relation to the number of IL-2 cycles a patient receives. There was also an absence of studies investigating sleep disturbance symptoms in patients receiving immunotherapy.

In conclusion, the trajectories, breadth, and depth of cognitive, affective, and sleep disturbance symptoms had yet to be described, which is essential for the
advancement of symptom science in IL-2 treatment, and thus became the focus of this dissertation.

6.1.2 Chapter 3: Evaluating Cognitive, Affective, and Sleep Disturbance Symptoms During High-Dose Interleukin-2 Therapy: A Case Study Approach

The study team began by examining the cognitive, affective, and sleep disturbance symptoms one MRCC patient receiving high-dose IL-2 experienced during one IL-2 treatment hospitalization in order to evaluate the feasibility and the methodology of using a case study approach to collect quantitative and qualitative data from the patient, the care partner, and the primary nurse as a case triad. Based on the feasibility evaluation of the methods in the pilot study, the study team made minor changes prior to enrollment for the larger scale study that explored ten IL-2 cases over all treatment doses (up to 14 per hospitalization) and over all treatment hospitalizations (up to four). Amendments to the study included: allowing for the enrollment of care partners who cannot be at the hospital fulltime but agreea to being an active participant in the index participant’s care (i.e. calling the patient and calling the nurses for updates), inclusion of a recorded semi-structured interview with the care partner at the post-treatment time point, the addition of two eight-item short-form self-report standardized measures evaluating anxiety and depressive symptoms completed by the index
participant at pre- and post-treatment, and allowing for the recorded semi-structured interview with the primary nurse to occur over the phone.

The study team concluded that the patient, care partner, and primary nurse case triad was feasible and provided the study team with rich, varied data that gave a picture of the patient’s cognitive, affective and sleep disturbance symptom trajectory over the course of one treatment. Qualitative reports of symptom change identified by the nurse and care partner enhanced and provided context to the patient scores on the quantitative standardized measures. Participants reported that the time required to complete semi-structured journal entries was minimal, feasible, and not burdensome. The recorded semi-structured interviews gave the study team the opportunity to ask follow-up questions to gather more explicit details (i.e. timing, frequency, duration, severity of symptoms) and seek clarity around ambiguous responses on journal entries.

The case study design allowed investigators to test data collection measures and explore the wide range of symptom trajectories in each case, while allowing for data saturation and triangulation. This case study highlighted how these methods can provide a unique and rich mechanism to collect quantitative and qualitative data from multiple case informants to gain a comprehensive picture of treatment and symptom trajectories that can be applied to other chronic illness populations where patients undergo aggressive treatment over multiple time points. Data gleaned from this
approach can help researchers and clinicians better understand their patient’s symptom trajectory and treatment experience, allowing for the design of tailored interventions to target unique challenges within each case.

6.1.3 Chapter 4: Trajectory of Cognitive Symptoms in Patients Receiving High-Dose Interleukin-2 Therapy

The study team described the trajectory of cognitive (inefficiencies or impairments in concentration, attention, short-term memory, executive functioning, abstraction, language, basic arithmetic, and orientation) symptoms within and across hospitalizations, collecting data from ten patients receiving IL-2, their care partners, and their primary nurses using a mixed-method case study approach for up to four hospitalizations for IL-2 therapy.

The study team sought to investigate:

- **Aim 1**: Transient and residual cognitive symptoms in patients receiving IL-2 during up to four hospitalizations for IL-2 therapy
- **Aim 2**: The patient’s transient and residual cognitive symptoms as qualitatively reported by each patient’s care partner and primary nurse during each hospital admission for IL-2 therapy
- **Aim 3**: The trajectory of transient and residual cognitive symptoms in patients receiving IL-2 over the total number of hospitalizations,
synthesizing patient data with care partner and nurse reports of symptom change

The study team chose three case exemplars with unique characteristics and attributes that best exemplify the diverse cognitive symptoms that patients receiving IL-2 experience to present the trajectory of the IL-2 cognitive symptom experience over the course of treatment. Many of the cognitive symptoms reported by the patient receiving IL-2, their care partner, their primary nurse and/or nurses through interviews or journals were not captured by the standardized measures given to the patients. Perhaps one of the reasons why cognitive symptoms often go unidentified and unmanaged is because clinicians do not recognize these cognitive symptoms and how they change over time. One of the reasons why these symptoms are overlooked is because clinicians do not administer standardized measures to patients receiving IL-2 to systematically assess for changes in cognition; however, these measurement tools were not accurate in assessing and detecting the full range of symptom alterations that were qualitatively reported by case informants.

Similarly, while the standardized measures often reflected minimal residual cognitive symptoms, indicating that index participants’ cognitive functioning returned to their baseline pre-treatment level, qualitative reports from patients, care partners, and nurses painted a different picture of the symptom trajectory and symptom experience.
Qualitative reports from case informants suggested that cognitive symptoms were interdependent and that these symptoms did have residual effects. For example, fatigue was the most frequently reported symptom by patients receiving IL-2 and was directly related to attentional function. While standardized measures did not indicate that patients receiving IL-2 experienced residual fatigue, patients and care partners reported that the level of fatigue experienced by the index participant rapidly increased with each subsequent dose of IL-2, suggesting a cumulative effect.

It is difficult to determine if fatigue was a result of the IL-2 treatment, a result of PRN medications, or a combination of both. However, fatigue co-occurred with other cognitive symptoms, such as decreased attention, altered memory, and confusion, and was particularly severe during physical symptoms such as rigors, which was likely a result of the high energy expenditure necessary to sustain their episodes of violent shaking. In a cohort of 200 women diagnosed with breast cancer who had surgery and received adjuvant chemotherapy, attentional function had a significant inverse correlation (p < 0.001) with anxiety, depression, fatigue, and sleep disturbance symptoms at all time points evaluated monthly, spanning from one month until 24 months after surgery (Chen et al., 2012). In other words, as attention function decreased, fatigue increased, and this report confirms our study team’s report of the
interdependence and synergistic effect of fatigue with other cognitive symptoms, as well as with affective and sleep disturbance symptoms.

Care partners identified and assisted in the management of cognitive alterations across the course of treatment. As treatment continued, care partners and patients learned how to co-manage the index participant’s cognitive symptoms and collaborated with nurses to prophylactically manage difficult symptoms. For example, patients and care partners learned that they were able to manage cognitive symptoms such as distractibility by getting rid of excess stimuli (i.e. turning TV off, putting away books), and/or postponing or skipping a dose of treatment. Care partners were invaluable in acting as a patient advocate, assisting in symptom management, and acting as a second set of ears when providers would do rounds but the patient was experiencing altered memory.

Although cognitive symptoms related to IL-2 treatment may not be eliminated, future interventions can be developed to help patients, care partners, and nurses manage these symptoms to improve the patient’s quality of life and treatment adherence. For example, psychosocial interventions such as hypnosis and cognitive behavioral therapy have been found to be very effective in the management of fatigue in cancer patients (Goedendorp, Gielissen, Peters, Verhagen, & Bleijenberg, 2012). Monthly one-hour cognitive behavioral therapy sessions were found to have a significant
reduction in fatigue in cancer patients actively receiving treatment, from the start of treatment up until seven months, and provided the most benefit to patients who experienced severe alterations in memory and attention (Goedendorp et al., 2012). Targeted interventions to manage fatigue and attention during aggressive treatment have the potential to minimize the cumulative effects of immunotherapy and reduce other cognitive, affective, and sleep disturbance symptoms.

The qualitative component of this study was crucial for the development of new cognitive symptom definitions, as well as re-defining our understanding of existing cognitive symptoms. These cognitive symptoms would have been overlooked and unidentified if the index participant was evaluated only with standardized measures. Because symptoms are synergistic and interdependent, a focus on fatigue management interventions could result in an overall improvement in cognitive symptoms. Potential future interventions could include both pharmacologic and alternative approaches initiated and/or driven by the patient, care partner, or nurse.

Current interventions used to manage cognitive alterations in other cancer cohorts receiving aggressive treatment that have shown a reduction in cognitive symptoms include computer-assisted cognitive training to improve executive functioning, memory, and processing speed (Treanor et al., 2016); yoga to reduce fatigue and improve sleep (Derry et al., 2015); and group and individual cognitive training (Von
Ah, Jansen, & Allen, 2014). There are mixed reviews surrounding the integrity of research studies designed to evaluate alternative approaches to manage cognitive symptoms, and therefore, mixed reviews on the true effectiveness of these interventions (Von Ah et al., 2014). Most published research evaluating the effectiveness of interventions targeting the improvement of cognitive symptoms has been conducted in the breast cancer population. Future research should focus on evaluating alternative approaches in other cancer populations, enrolling larger sample sizes, and investigating underlying causes of cognitive alterations such as why certain individuals are more susceptible to cognition symptoms. Perhaps there is a genetic component, and individuals who are susceptible to severe alterations have a single nucleotide polymorphism increasing his or her risk for such cognitive alterations (Von Ah et al., 2014).

6.1.4 Chapter 5: Trajectory of Affective and Sleep Symptoms in Patients Receiving High-Dose Interleukin-2 Therapy

The study team described the trajectory of affective (mood alterations, depression, anxiety, aggression, and suicidal ideation) and sleep disturbance (insomnia and hypersomnia) symptoms within and across hospitalizations, collecting data from ten patients receiving IL-2, their care partners and their primary nurses using a mixed-method case study approach for up to four hospitalizations for IL-2 therapy. Three case exemplars with unique characteristics and attributes that best exemplify the diverse...
affective and sleep disturbance symptoms experienced by patients receiving IL-2 were chosen to present the trajectory of the IL-2 affective and sleep disturbance symptom experience over the course of treatment.

This chapter sought to:

• **Aim 1**: Describe transient and residual affective (depression, anxiety, mood alterations), and sleep disturbance (insomnia, hypersomnia) symptoms in patients receiving IL-2 during up to four hospitalizations for IL-2 therapy

• **Aim 2**: Describe transient and residual affective and sleep disturbance symptoms as qualitatively reported by each patient’s care partner, and primary nurse during each hospital admission for IL-2 therapy

• **Aim 3**: Describe the trajectory of transient and residual affective and sleep disturbance symptoms in patients receiving IL-2 over the total number of hospitalizations, synthesizing patient data with care partner and nurse reports of symptom change

See Section 6.1.3 for detail about the benefit of a case study approach when evaluating the symptom experience of patients receiving IL-2 and for the importance of qualitative research methods to form new understandings of the affective and sleep disturbance symptom experience. Similar to qualitative evaluations of cognitive
symptoms, qualitative reports of affective and sleep disturbance symptoms enabled researchers to develop new symptom definitions that more accurately described the symptom experience patients reported.

Of particular importance is the concept of anticipatory anxiety, which emerged in multiple cases and was incapacitating to patients. Patients reported watching the clock in anticipation of the onset of their rigors after receiving their dose of IL-2. With this increase in anxiety, patients reported also experiencing sleep alterations and decreased attentional function. Anticipatory anxiety was prevalent in a large subset of the study sample, yet our study team would have been unaware of this symptom if qualitative reports for the patient, care partner, and nurse were not included in the data collection methods because standardized measures did not screen for or assess this specific type of anxiety. While concepts such as anticipatory nausea have been described in the oncology population (Ameringer et al., 2013), anticipatory anxiety has not been. Qualitative reports from care partners and nurses suggest that anticipatory anxiety worsens the anxiety symptom experience, and because symptoms are synergistic and interdependent, affective symptoms also worsen.

Similarly, while the IDS-C sleep disturbance subscale quantified the “level” of sleep disturbance severity, without qualitative reports, the study team would have been unable to identify what these sleep disturbance symptoms looked like over the
treatment trajectory. For example, sleep disturbance most frequently presented as decreased and/or restless sleep early in the treatment cycle; however, in the large majority of cases, patients experienced a state of hypersomnia towards the end of treatment. For example, one index participant reported that he slept more than 20 hours within a 24-hour period on his last day of treatment. This change from insomnia at the beginning of the treatment cycle to hypersomnia towards the end is likely due to the cumulative effect that IL-2 has on the body, and as the patient receives more doses of IL-2, he or she continues to experience greater residual effects from previous doses. Importantly, researchers have found that there is an association between global sleep quality and affective symptoms such as depression and anxiety in the older adult population (Gould et al., 2018). In other words, as sleep quality decreases, affective symptoms increase. In a cohort of approximately 100 women diagnosed with breast cancer, researchers found that fatigue was significantly correlated with sleep disturbance and depression (Bower et al., 2011). Designing interventions to target sleep disturbance symptoms may be essential in minimizing cognitive symptoms such as fatigue and affective symptoms such as depression and anxiety.

6.2 Limitations

This study was exploratory in nature, and therefore, the study sample size was limited. Although the study sample was representative of the IL-2 population at the
teaching hospital, the index participant sample was rather homogenous, lacking racial and ethnic representation.

Both the self-report PROMIS-8a measure evaluating anxiety and the self-report PROMIS-8b measure evaluating depression showed vastly different trends in the symptom trajectory experience when compared to the clinician-rated standardized measures HAM-A and IDS-C evaluating anxiety and depression, respectively. These differences could be because the measurement scales were too abbreviated for this population or because the index participants were not able to self-identify/self-recognize alterations in symptoms over the treatment trajectory. While some patients were aware of their symptom experiences, others heavily relied on their care partners to fill in the gaps as to what they experienced and when, showing the value of the care partner residing at the bedside during aggressive treatment.

6.3 Future Directions of Research

6.3.1 Implications for Nursing Practice

Nurses are at the forefront of coordinating care among patients, care partners, and the healthcare team, and therefore play a key role in translating research into practice. Patients and care partners reported confusion and frustration surrounding the inconsistent verbiage used by the healthcare team when discussing treatment with IL-2. Education should be provided to nurses and healthcare providers about using language
that is uniform when discussing treatment with IL-2. Along these same lines, inaccurate information was relayed to patients and care partners about the number of doses necessary to elicit a response to IL-2 treatment. As a result, patients and care partners reported feelings of disappointment and failure if they did not receive “enough” IL-2 doses because patients were told that more doses of treatment correlates to better treatment responses. However, this correlation did not hold true in the ten cases in this study. Education should be provided to nurses and the healthcare team to ensure appropriate and accurate information is provided to patients and their care partners. Nurses are also responsible for assessing patients for symptom change. In addition to keen assessment skills, nurses should also determine if there are any pro re nata (PRN) medications that might be contributing to or exacerbating these alterations, for example the use of Lorazepam to assist with sleep and anxiety.

Similarly, because care partners are most familiar with the patients (i.e. how they function at their baseline, identifying deviations from baseline functioning), they are the first line of defense when assessing for acute changes in cognition, affect, and sleep, and the importance of their roles should be maximized. It is important to educate patients and their care partners about the wide array of symptom alterations that can occur over the course of treatment as well as their prevalence and severities. Education about what and when to expect specific symptoms can lower anxiety levels for the patient and their
care partner. For example, nurses could provide the following explanation of the symptoms that patients receiving IL-2 can expect:

Patients may initially experience low levels of fatigue and insomnia. As patients receive more doses of IL-2, fatigue will increase and patients will likely experience hypersomnia by their last day of treatment. Rigors typically occur two to four hours after the IL-2 dose is administered, and these rigor episodes result in large energy expenditure. Therefore, more severe episodes will result in more severe fatigue, which in turn can result in cognitive alterations such as altered short-term memory, decreased attention, and confusion.

Education about the illness trajectory and what to expect during and after treatment has been shown to help care partners and patients set realistic shared expectations, increase coping mechanisms, and decrease feelings of powerlessness in the cancer population (Whisenant, 2011; Williams, 2007).

Our study confirmed that alterations in cognition, affect, and sleep in high-dose IL-2 therapy is multifaceted, meaning that these alterations might be the result of any or all of these factors including fluid overload, IL-2 crossing the blood brain barrier, or the many concomitant medications used to reduce other severe side effects of IL-2 treatment (Schwartz et al., 2002). Importantly, because these symptoms are often interdependent and cumulative, reduction of symptoms such as fatigue may also concordantly improve depressive symptoms, anxiety, sleep, cognitive alterations and quality of life.
6.3.2 Implications for Research

Although often deemed subpar to quantitative research, qualitative research is important to understand the lived symptom and treatment experience of cancer patients receiving aggressive treatment and is important for truly grasping the treatment trajectory so appropriate interventions can be developed and introduced at the most critical times (Florczak, 2017). For example, attentional fatigue in breast cancer patients was associated with negative outcomes such as higher prevalence of affective symptoms (i.e. depression) (Von Ah et al., 2017), so key interventions would focus on addressing and managing the level of fatigue these patients experience.

Future studies should focus on exploring symptoms that emerged qualitatively in this study (i.e. anticipatory anxiety) as well as exploring symptoms that were re-defined (i.e. decreased/restless sleep towards the beginning of treatment and increased sleep/hypersomnia towards the end of treatment, fatigue, and attentional function) in a larger patient population to better understand the trajectory of symptoms across the treatment course. After gaining a better understanding of the symptom trajectory in a larger population, individualized interventions should be developed to merge the detrimental gap between research and clinical practice, ultimately translating science into practice.
A case study design allowed the study team to gain an in-depth understanding of the wide range of cognitive, affective, and sleep disturbance symptoms experienced across the treatment trajectory for each unique case while allowing for data saturation and triangulation. This mixed-method case study approach allowed the study team to capture data to support the creation of new symptom definitions as well as modify our understanding of known symptoms (i.e. symptoms the study team found in the literature) in the IL-2 population. Patients in other chronic illness populations likely experience dose-limiting symptoms that go unidentified and unmanaged. The methodology used in this dissertation can be applied to other chronic illness populations where patients undergo aggressive treatment over multiple time points to help researchers and clinicians better understand their patient’s symptom trajectory and treatment experience and therefore design tailored interventions to target unique challenges within each individual case.

6.4 Conclusion

Understanding the trajectory and temporal relationship of cognitive, affective, and sleep disturbance symptoms can help researchers to develop interventions to ameliorate symptoms and improve treatment tolerance, remission rates, and quality of life. Trajectory analysis is a powerful method to deconstruct symptom changes associated with cyclic dosing therapy, such as IL-2 therapy, because symptom responses
are often cumulative and intensify over time (Dutcher et al., 2014). Cognitive, affective, and sleep disturbance symptoms can be interdependent and appear in unique clusters for each patient. Analyzing details of symptom groups during treatments within and across hospitalizations allows researchers to identify patterns in symptom appearance, intensity, and interdependence (Henly et al., 2011).

Future research could benefit from using this methodology in other chronic illness patient populations to better understand the trajectory of their symptoms and how they change over time. Points of trajectory change are potential time points where future interventions could be introduced to manage IL-2-induced symptoms, or symptoms secondary to other aggressive treatment. Furthermore, unique interventions can target each case informant to best help the patient undergoing treatment. Future research can investigate whether certain subgroups of patients are susceptible to specific symptom clusters, if there is a genetic link to the symptoms experienced by patients, and if interventions targeting the reduction of prevalent and severe symptoms such as fatigue, sleep disturbance, and anxiety also result in a reduction of symptoms across all symptom domains.
Appendix A: Demographics Forms

Part I: Patient Demographics Form

Initials: __ __ __
Participant ID: __ __ __
Gender:
  __ Male
  __ Female
Race:
  __ American Indian or Alaska Native
  __ Asian
  __ Black or African American
  __ Native Hawaiian or Other Pacific Islander
  __ White
  __ Other: ___________
  __ Refuse to answer
Ethnicity:
  __ Hispanic
  __ Non Hispanic or Latino
  __ Refuse to answer
Age: ___________
Marital Status:
  __ Single
  __ Married
  __ Divorced
  __ Widowed
Previous cancer treatments: _______________
When were you diagnosed? _______________
What is your relationship to your care partner? _______________
How long have you known your care partner? _______________
How long has your care partner been caring for you? _______________
Part II: Care Partner Demographics Form

Initials: __ __ __
Participant ID: __ __ __
Gender:
  __ Male
  __ Female
Race:
  __ American Indian or Alaska Native
  __ Asian
  __ Black or African American
  __ Native Hawaiian or Other Pacific Islander
  __ White
  __ Other: ___________
  __ Refuse to answer
Ethnicity:
  __ Hispanic
  __ Non Hispanic or Latino
  __ Refuse to answer
Age: ___________
Marital Status:
  __ Single
  __ Married
  __ Divorced
  __ Widowed
Relationship to Patient: ________________
How many years have you known the patient? ________________
How many years have you been caring for the patient? ________________
Part III: Primary Nurse Demographics Form

Initials: __ __ __
Participant ID: __ __ __
Gender:
__ Male
__ Female
Race:
__ American Indian or Alaska Native
__ Asian
__ Black or African American
__ Native Hawaiian or Other Pacific Islander
__ White
__ Other: ___________
__ Refuse to answer
Ethnicity:
__ Hispanic
__ Non Hispanic or Latino
__ Refuse to answer
Age: ___________
Marital Status:
__ Single
__ Married
__ Divorced
__ Widowed
How many years have you been working as a nurse? _____________
How many years have you worked in oncology? ________________
How long did you care for the patient? ________________
How long have you been caring for IL-2 patients? ________________
Appendix B: Measurement Tools

Part I: Attentional Function Index (AFI)

<table>
<thead>
<tr>
<th>Investigating Cognitive/Affective/Sleep Symptoms in Patients Receiving High-Dose Interleukin-2 Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attentional Function Index (AFI)</td>
</tr>
<tr>
<td>Patient Number: __ __ __</td>
</tr>
<tr>
<td>Hospital Admission: __</td>
</tr>
<tr>
<td>Baseline: Y/N</td>
</tr>
<tr>
<td>Patient Initials: __ __ __</td>
</tr>
<tr>
<td>Date: __ / __ / ____</td>
</tr>
<tr>
<td>Doses Completed:</td>
</tr>
</tbody>
</table>

| Section I:                                                                                              |
| At this time, how well do you feel that you are functioning in each of the areas below? Place a mark through the line at whatever point best describes how you are doing in each area at present. |

| Note: Lines are scales 1 to 100 in increments of 5. |

| 1. Getting started on activities (tasks, jobs) you intend to do.                                      |
| Not at all | Extremely well |
| 2. Following through on your plans.                                                                  |
| Not at all | Extremely well |
| 3. Doing things that take time and effort.                                                            |
| Not at all | Extremely well |
| 4. Making your mind up about things.                                                                  |
| Not at all | Extremely well |
| 5. Keeping your mind on what you are doing.                                                           |
| Not at all | Extremely well |
| 6. Remembering to do all the things you started out to do.                                            |
| Not at all | Extremely well |
7. Keeping your mind on what others are saying.

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Extremely well</th>
</tr>
</thead>
</table>

8. Keeping yourself from saying or doing things you did not want to say or do.

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Extremely well</th>
</tr>
</thead>
</table>


<table>
<thead>
<tr>
<th>Not at all</th>
<th>Extremely well</th>
</tr>
</thead>
</table>

Section II: At this time, how would you rate yourself on:

10. How hard you find it to concentrate on details.

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Extremely</th>
</tr>
</thead>
</table>

11. How often do you make mistakes on what you are doing.

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Extremely</th>
</tr>
</thead>
</table>

12. Forgetting to do important things.

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Extremely</th>
</tr>
</thead>
</table>

13. Getting easily annoyed or irritated.

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Extremely</th>
</tr>
</thead>
</table>
Part II: Hamilton Anxiety Scale (HAM-A)

<table>
<thead>
<tr>
<th>Hamilton Anxiety Scale (HAM-A)--14 Item</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Number:</strong> ___ ___ ___</td>
</tr>
<tr>
<td><strong>Patient Initials:</strong> ___ ___ ___</td>
</tr>
</tbody>
</table>

Below is a list of phrases that describe certain feeling that people have. Rate the patients by finding the answer which best describes the extent to which he/she has these conditions. Select one of the five responses for each of the fourteen questions.

<table>
<thead>
<tr>
<th>Question</th>
<th>Description</th>
<th>Response 0</th>
<th>Response 1</th>
<th>Response 2</th>
<th>Response 3</th>
<th>Response 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Anxious Mood:</td>
<td>Worries, anticipation of the worst, fearful anticipation, irritability.</td>
<td>Not Present</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Very Severe/Incapacitating</td>
</tr>
<tr>
<td>2. Tension:</td>
<td>Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax. How many days? How long do sx last? How severe?</td>
<td>Not Present</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Very Severe</td>
</tr>
<tr>
<td>3. Fears:</td>
<td>Of dark, of strangers, of being left alone, of animals, of traffic, of crowds. Do you have any &quot;scaredness&quot;-- Do you have any phobias?</td>
<td>Not Present</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Very Severe</td>
</tr>
<tr>
<td>4. Insomnia:</td>
<td>Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors.</td>
<td>Not Present</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Very Severe</td>
</tr>
<tr>
<td>5. Intellectual:</td>
<td>Difficulty in concentration, poor memory.</td>
<td>Not Present</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Very Severe</td>
</tr>
<tr>
<td>6. Depressed Mood:</td>
<td>Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing.</td>
<td>Not Present</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Very Severe</td>
</tr>
</tbody>
</table>
7. Somatic (Muscular):
Pains and aches, twiching, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Not Present</td>
</tr>
<tr>
<td>1</td>
<td>Mild</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
</tr>
<tr>
<td>4</td>
<td>Very Severe</td>
</tr>
</tbody>
</table>

8. Somatic (Sensory):
Tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking sensation, electrical pulsing.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Not Present</td>
</tr>
<tr>
<td>1</td>
<td>Mild, minimal</td>
</tr>
<tr>
<td>2</td>
<td>Moderate, half the time</td>
</tr>
<tr>
<td>3</td>
<td>Severe, more than half of the time</td>
</tr>
<tr>
<td>4</td>
<td>Very Severe</td>
</tr>
</tbody>
</table>

9. Cardiovascular Symptoms:
Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat. If heart condition, score 0.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Not Present</td>
</tr>
<tr>
<td>1</td>
<td>Mild</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
</tr>
<tr>
<td>4</td>
<td>Very Severe</td>
</tr>
</tbody>
</table>

10. Respiratory Symptoms:
Pressure or constriction in chest, choking feelings, sighing, dyspnea. If lung condition, score 0.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Not Present</td>
</tr>
<tr>
<td>1</td>
<td>Mild</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
</tr>
<tr>
<td>4</td>
<td>Very Severe</td>
</tr>
</tbody>
</table>

11. Gastrointestinal Symptoms:
Difficulty in swallowing, wind abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, gas, looseness of bowels, loss of weight, constipation.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Not Present</td>
</tr>
<tr>
<td>1</td>
<td>Mild</td>
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<tr>
<td>2</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
</tr>
<tr>
<td>4</td>
<td>Very Severe</td>
</tr>
</tbody>
</table>

12. Genitourinary Symptoms:
Frequency of urination, urgency of urination, amenorrhea (no period), menorrhagia (heavy/long period), development of frigidity, premature ejaculation, loss of libido, impotence.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>0</td>
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<tr>
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<tr>
<td>2</td>
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<tr>
<td>3</td>
<td>Severe</td>
</tr>
<tr>
<td>4</td>
<td>Very Severe</td>
</tr>
</tbody>
</table>

13. Autonomic Symptoms:
Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<tr>
<td>1</td>
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<tr>
<td>2</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
</tr>
<tr>
<td>4</td>
<td>Very Severe</td>
</tr>
</tbody>
</table>

14. Behavior at Interview:
Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, etc.

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<tr>
<th>Score</th>
<th>Description</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
<td>3</td>
<td>Severe</td>
</tr>
<tr>
<td>4</td>
<td>Very Severe</td>
</tr>
</tbody>
</table>

HAM-A Total Score:
Part III: Inventory of Depressive Symptomatology-Clinician Rated (IDS-C)

<table>
<thead>
<tr>
<th>Investigating Cognitive/Affective/Sleep Symptoms in Patients Receiving High-Dose Interleukin-2 Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inventory of Depressive Symptomatology (IDS-C)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient Number: __ __ __</th>
<th>Hospital Admission: __</th>
<th>Baseline: Y/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Initials: __ __ __</td>
<td>Date: __ / __ / _____</td>
<td>Doses Completed: __</td>
</tr>
</tbody>
</table>

Please check one response to each item that best describes the patient for the last seven days:

1. **Sleep Onset Insomnia**: How have you been sleeping in the past week? Have you had trouble falling asleep when you go to bed? Right after you go to bed, how long does it take you to fall asleep? How many days in the past week have you had trouble falling asleep?

   - **0** = Never take longer than 30 minutes to fall asleep.
   - **1** = Takes at least 30 minutes to fall asleep, less than half the time.
   - **2** = Takes at least 30 minutes to fall asleep, more than half the time.
   - **3** = Takes more than 60 minutes to fall asleep, more than half the time.

2. **Mid-Nocturnal Insomnia**: During the past week, have you been waking in the middle of the night? If YES: How long do you stay awake? Do you get out of bed? Are you able to fall right back to sleep? If NO insomnia: Has your sleep been restless or disturbed some nights?

   - **0** = Does not wake up at night.
   - **1** = Restless, light sleep with few awakenings.
   - **2** = Wakes up at least once a night, but goes back to sleep early.
   - **3** = Awakens more than once a night and stays awake for 20 minutes or more, more than half the time.

3. **Early Morning Insomnia**: What time have you been waking up in the past week? With or without an alarm? Is this earlier than is normal for you? How many days in the past week? Are you able to go back to sleep?

   - **0** = Less than half the time, awakens no more than 30 minutes before necessary.
   - **1** = More than half the time, awakens more than 30 minutes before need be.
   - **2** = Awakens at least one hour before need be, more than half the time.
   - **3** = Awakens at least two hours before need be, more than half the time.

4. **Hypersomnia**: How many hours on average have you been sleeping in a 24-hour period in the past week, including naps? What is the longest you’ve slept in a 24-hour period last week?

   - **0** = Sleeps no longer than 7-8 hours/night, without naps.
   - **1** = Sleeps no longer than 10 hours in a 24 hour period (including naps).
   - **2** = Sleeps no longer than 12 hours in a 24 hour period (including naps).
   - **3** = Sleeps longer than 12 hours in a 24 hour period (including naps).

5. **Mood (Sad)**: How would you describe your mood in the past week? Have you been feeling down, blue, sad or depressed? In the past week, how much of the time have you felt ________?

   - **0** = Does not feel sad.
   - **1** = Feels sad less than half the time.
   - **2** = Feels sad more than half the time.
   - **3** = Feels intensely sad virtually all of the
### 6. Mood (Irritable): Have you felt irritable in the past week? Have you found yourself becoming more easily angered or irritated by others? How much of the time in this past week?

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>Does not feel irritable.</td>
</tr>
<tr>
<td>1</td>
<td>Feels irritable less than half of the time.</td>
</tr>
<tr>
<td>2</td>
<td>Feels irritable more than half of the time.</td>
</tr>
<tr>
<td>3</td>
<td>Feels extremely irritable virtually all of the time.</td>
</tr>
</tbody>
</table>

### 7. Mood (Anxious): Have you been feeling especially anxious, nervous or on edge in the past week? How much of the time in this past week, have you felt irritable? Every day? (READ LIST, pausing after each symptom for a reply. When sx(s) are endorsed, ask follow-up questions).

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>Does not feel anxious or tense.</td>
</tr>
<tr>
<td>1</td>
<td>Feels anxious/tense less than half of the time.</td>
</tr>
<tr>
<td>2</td>
<td>Feels anxious/tense more than half of the time.</td>
</tr>
<tr>
<td>3</td>
<td>Feels extremely anxious/tense virtually all of the time.</td>
</tr>
</tbody>
</table>

### 8. Reactivity of Mood: In the past week, when something good, even small things have happened, did your mood brighten up? How long did this brightened mood last? Were there things that occurred that should have brightened your mood but did not?

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<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Mood brightens to normal level and lasts several hours when good events occur.</td>
</tr>
<tr>
<td>1</td>
<td>Mood brightens but does not feel like normal self when good events occur.</td>
</tr>
<tr>
<td>2</td>
<td>Mood brightens only somewhat with few selected, extremely desired events.</td>
</tr>
<tr>
<td>3</td>
<td>Mood does not brighten at all, even when very good or desired events occur.</td>
</tr>
</tbody>
</table>

### 9. Mood Variation: In the past week, have you noticed feeling worse at any particular time of the day—such as in the morning or evening? (IF YES), is this related to any particular events(s)? How much worse do you feel—a little bit or a lot? Even on weekends?

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Notes no regular relationship between mood and time of day.</td>
</tr>
<tr>
<td>1</td>
<td>Mood often relates to time of day due to environmental circumstances.</td>
</tr>
<tr>
<td>2</td>
<td>For most of the week, mood appears more related to time of day than to events.</td>
</tr>
<tr>
<td>3</td>
<td>Mood is clearly, predictably, better or worse at fixed time each day.</td>
</tr>
</tbody>
</table>

### 9A. Is mood typically worse: in the morning, afternoon or night (circle one).

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Mood is virtually identical to feelings associated with bereavement or is undisturbed.</td>
</tr>
<tr>
<td>1</td>
<td>Mood is largely like sadness in bereavement, although it may lack explanation, be associated with more anxiety, or be much more intense.</td>
</tr>
<tr>
<td>2</td>
<td>Less than half the time, mood is qualitatively distinct from grief and therefore difficult to explain to others.</td>
</tr>
<tr>
<td>3</td>
<td>Mood is qualitatively distinct from grief nearly all of the time.</td>
</tr>
</tbody>
</table>

### 9B. Is mood variation attributed to environment by the patient: yes, or no (circle one).

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No change from usual appetite.</td>
</tr>
<tr>
<td>1</td>
<td>Eats somewhat less often and/or lesser amounts than usual.</td>
</tr>
</tbody>
</table>

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Complete either 11 or 12
<table>
<thead>
<tr>
<th>Question</th>
<th>Response Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>reminded you to eat?</td>
<td>2 = Eats much less than usual and only with personal effort.</td>
</tr>
<tr>
<td></td>
<td>3 = Eats rarely within a 24-hour period, and only with extreme personal effort with persuasion by others.</td>
</tr>
<tr>
<td><strong>12. Appetite (Increased):</strong> Have you found yourself eating more than usual? Have you felt driven to eat? Have you had eating binges?</td>
<td>0 = No change from usual appetite.</td>
</tr>
<tr>
<td></td>
<td>1 = More frequently feels a need to eat than usual.</td>
</tr>
<tr>
<td></td>
<td>2 = Regularly eats more often and/or greater amounts than usual.</td>
</tr>
<tr>
<td></td>
<td>3 = Feels driven to overeat at and between meals.</td>
</tr>
<tr>
<td><strong>13. Weight (Decrease) Within the Last Two Weeks:</strong></td>
<td>0 = Has experienced no weight change.</td>
</tr>
<tr>
<td>Omit</td>
<td>1 = Feels as if some slight weight loss has occurred.</td>
</tr>
<tr>
<td></td>
<td>2 = Has lost 2 pounds or more.</td>
</tr>
<tr>
<td></td>
<td>3 = Has lost 5 pounds or more.</td>
</tr>
<tr>
<td><strong>14. Weight (Increase) Within the Last Two Weeks:</strong></td>
<td>0 = Has experienced no weight change.</td>
</tr>
<tr>
<td>Omit</td>
<td>1 = Feels as if some slight weight gain has occurred.</td>
</tr>
<tr>
<td></td>
<td>2 = Has gained 2 pounds or more.</td>
</tr>
<tr>
<td></td>
<td>3 = Has gained 5 pounds or more.</td>
</tr>
<tr>
<td>**15. Concentration/Decision: How has your concentration been in the past week? Were you able to focus on what you were doing (like reading or watching TV)? Did you notice that minor decisions were more difficult to make than usual (what to wear, eat, watch on TV)?</td>
<td>0 = No change in usual capacity to concentrate and decide.</td>
</tr>
<tr>
<td></td>
<td>1 = Occasionally feels indecisive or notes that attention often wanders.</td>
</tr>
<tr>
<td></td>
<td>2 = Most of the time struggles to focus attention or make decisions.</td>
</tr>
<tr>
<td></td>
<td>3 = Cannot concentrate well enough to read or cannot make even minor decisions.</td>
</tr>
<tr>
<td>**16. Outlook (Self): In the past week, how have you felt about yourself? Have you been down on yourself in the past week? More than is normal for you? Have you been feeling guilty? Do you feel like you’re being punished? Have your noticed your self-esteem has been down in the past week? How would you rate your worth as a person compared to others?</td>
<td>0 = Sees self as equally worthwhile and deserving as others.</td>
</tr>
<tr>
<td></td>
<td>1 = Is more self-blaming than usual.</td>
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<tr>
<td></td>
<td>2 = Largely believes that he/she causes problems for others.</td>
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<tr>
<td></td>
<td>3 = Ruminates over major and minor defects in self.</td>
</tr>
<tr>
<td>**17. Outlook (Future): How have you been feeling about the future? (optimistic/pessimistic) Do you feel better with encouragement/reassurance from others? Do you feel things will get better, improve, work out?</td>
<td>0 = Views future with usual optimism.</td>
</tr>
<tr>
<td></td>
<td>1 = Occasionally has pessimistic outlook that can be dispelled by others or events.</td>
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<tr>
<td></td>
<td>2 = Largely pessimistic for the near future.</td>
</tr>
<tr>
<td></td>
<td>3 = Sees no hope for self/situation anytime in the future.</td>
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<tr>
<td><strong>18. Suicidal Ideation: In the past week, have you felt that life was not worth living? Do you</strong></td>
<td>0 = Does not think of suicide or death.</td>
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<tr>
<td></td>
<td>1 = Feels life is empty or is not worth living.</td>
</tr>
<tr>
<td>Question</td>
<td>Rating 0</td>
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<tr>
<td>-------------------------------------------------------------------------</td>
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<tr>
<td>Have thoughts of death or suicide? How often do these thoughts come?</td>
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<tr>
<td>How long do they stay? What have you thought about? Have you thought</td>
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<tr>
<td>of a plan in the last week? Have you done anything to hurt yourself?</td>
<td></td>
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<tr>
<td>2 = Thinks of suicide/death several times a week for several minutes.</td>
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<tr>
<td>3 = Thinks of suicide/death several times a day in depth, or has</td>
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<tr>
<td>made specific plans, or attempted suicide.</td>
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<tr>
<td>19. Involvement: How have you been spending your time this last week?</td>
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<tr>
<td>(when not at home)? Is that normal for you? Have you stopped doing</td>
<td></td>
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<tr>
<td>anything you used to do? How would you describe your level of interest</td>
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<tr>
<td>and motivation to complete daily activities? Do you feel you have to</td>
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<tr>
<td>push yourself? Is there anything you look forward to or still enjoy?</td>
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</tr>
<tr>
<td>0 = No change from usual level of interest in other people and activities.</td>
<td></td>
</tr>
<tr>
<td>1 = Notices a reduction in former interests/activities.</td>
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<tr>
<td>2 = Finds only one or two former interests remain.</td>
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</tr>
<tr>
<td>3 = Has virtually no interest in formerly pursued activities.</td>
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<tr>
<td>20. Energy/Fatigability: How has your energy been this past week?</td>
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<tr>
<td>Have you noticed that you tire more easily than you used to? Have you</td>
<td></td>
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<tr>
<td>been tired all the time?</td>
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</tr>
<tr>
<td>0 = No change in usual level of energy.</td>
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<tr>
<td>1 = Tires more easily than usual.</td>
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</tr>
<tr>
<td>2 = Makes significant personal effort to initiate or maintain usual</td>
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<tr>
<td>daily activities.</td>
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<td>3 = Unable to carry out most of usual daily activities due to lack of</td>
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<tr>
<td>energy.</td>
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<tr>
<td>21. Pleasure/Enjoyment (exclude sexual activity): Have you had any fun</td>
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<tr>
<td>this past week? Has there been anything you enjoyed (meal, movie,</td>
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<tr>
<td>spending time with friends)? (IF YES), was the enjoyment you</td>
<td></td>
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<tr>
<td>experienced at a normal level for you? (IF NO), if you had a chance to</td>
<td></td>
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<tr>
<td>have fun, do you think that you would enjoy yourself?</td>
<td></td>
</tr>
<tr>
<td>0 = Participates in and derives usual sense of enjoyment from</td>
<td></td>
</tr>
<tr>
<td>pleasurable activities.</td>
<td></td>
</tr>
<tr>
<td>1 = Does not feel usual enjoyment and pleasurable activities.</td>
<td></td>
</tr>
<tr>
<td>2 = Rarely derives pleasure from any activities.</td>
<td></td>
</tr>
<tr>
<td>3 = Is unable to register any sense of pleasure/enjoyment from anything.</td>
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<tr>
<td>22. Sexual Interest: How has your interest in sex been in the past</td>
<td></td>
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<tr>
<td>week (not activity or opportunity, but your level of interest)? Has</td>
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<tr>
<td>there been any change in your interest (from when you were not</td>
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<td>depressed)? Is sex something you’ve thought about this week? Is that</td>
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<tr>
<td>unusual for you?</td>
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<tr>
<td>0 = Has usual interest in or derives usual pleasure from sex.</td>
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<tr>
<td>1 = Has near usual interest in or derives some pleasure from sex.</td>
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</tr>
<tr>
<td>2 = Has little desire for or rarely derives pleasure from sex.</td>
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</tr>
<tr>
<td>3 = Has absolutely no interest in or derives no pleasure from sex.</td>
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<tr>
<td>23. Psychomotor: Have you felt slowed down in your thinking, speaking,</td>
<td></td>
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<tr>
<td>or movement in the past week? Have others commented on this? (RATING</td>
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<tr>
<td>BASED ON OBSERVATION DURING INTERVIEW AND PATIENT SELF-REPORT.)</td>
<td></td>
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<tr>
<td>0 = Normal speed of thinking, gesturing and speaking.</td>
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<tr>
<td>1 = Patient notes slowed thinking, and voice modulation is reduced.</td>
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</tr>
<tr>
<td>2 = Takes several seconds to respond to most questions; reports slowed</td>
<td></td>
</tr>
<tr>
<td>thinking.</td>
<td></td>
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<tr>
<td>3 = Is largely unresponsive to most questions without strong</td>
<td></td>
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<tr>
<td>encouragement.</td>
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<tr>
<td>24. Psychomotor Agitation: Have you noticed feeling restless or</td>
<td></td>
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<tr>
<td>fidgety in the past week? Have you found yourself unable to stay</td>
<td></td>
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<td>seated or needing to move around? (RATING BASED</td>
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## ON OBSERVATION DURING INTERVIEW AND PATIENT SELF-REPORT.

| 25. Somatic Complaints: How has your energy been in the past week? In the past week, have you found that you tire more easily than usual? Have you been tired all the time? In the past week, have you had any backaches, headaches, muscle aches or heaviness in your head or limbs? | 2 = Describes impulse to move about and displays motor restlessness.  
3 = Unable to stay seated. Paces about with or without permission. |
| --- | --- |
| 0 = States there is no feeling of limb heaviness or pains. | 1 = Complains of headaches, abdominal, back or joint pains that are intermittent and not disabling.  
2 = Complains that the above pains are present most of the time.  
3 = Functional impairment results from the above pain. |
| 26. Sympathetic Arousal: Palpitations, tremors, blurred vision, tinnitus, increased sweating, shortness of breath, hot/cold flashes, chest pain. In the past week, have you any of the following symptoms (READ LIST, pausing after each symptom for a reply). How much have these things been bothering you in the past week? How bad have they gotten? How much time have you had them? | 0 = Reports no palpitations, tremors, blurred vision, tinnitus or increased sweating, dyspnea, hot and cold flashes, chest pain.  
1 = The above are mild and only intermittently present.  
2 = The above are moderate and present more than half the time.  
3 = The above result in functional impairment. |
| 27. Panic/Phobic Symptoms: Have you suddenly felt intensely frightened, anxious or extremely uncomfortable? Extremely panicky for no apparent reason? Has this occurred in the past 7 days? When did it last occur? What happened? Are there situations or things that you persistently dislike or avoid because they make you anxious? Any phobias? Have you noticed this avoidance increasing in the past week? | 0 = Has neither panic episodes nor phobic symptoms.  
1 = Has mild panic episodes or phobias that do not usually alter behavior or incapacitate.  
2 = Has significant panic episodes or phobias that modify behavior or incapacitate.  
3 = Has incapacitating panic episodes at least once a week or severe phobias that lead to complete and regular avoidance behavior. |
| 28. Gastrointestinal: How much have these things been bothering you in the past week? How bad have they gotten? How much time have you had them? | 0 = Has no change in usual bowel habits.  
1 = Has intermittent constipation and/or diarrhea that is mild.  
2 = Has diarrhea and/or constipation most of the time that does not impair functioning.  
3 = Has intermittent presence of constipation and/or diarrhea that requires treatment or causes functional impairment. |
| 29. Interpersonal Sensitivity: Have you felt easily rejected, slighted or criticized by others? How often has this occurred? How do you respond when that happens—angry, down, etc.? (Probe severity of reaction) How does this impact upon your ability to relate with others socially or complete work tasks? | 0 = Has not felt easily rejected, slighted, criticized or hurt by others at all.  
1 = Occasionally feels rejected, slighted, criticized or hurt by others.  
2 = Often feels rejected, slighted, criticized or hurt by others, but with only slight effects on social/occupational functioning. |
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<table>
<thead>
<tr>
<th><strong>30. Leaden Paralysis/Physical Energy:</strong> During the past week, have you had feelings of being weighted down, like you had lead weights on your arms and legs? How many days? How much of the time? Do these symptoms interfere with your day-to-day activities?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3</strong> = Often feels rejected, slighted, criticized or hurt by others that results in impaired social/occupational functioning.</td>
</tr>
<tr>
<td><strong>0</strong> = Does not experience the physical sensation of feeling weighted down and without physical energy.</td>
</tr>
<tr>
<td><strong>1</strong> = Occasionally experiences periods of feeling physically weighed down and without physical energy, but without a negative effect on work, school or activity.</td>
</tr>
<tr>
<td><strong>2</strong> = Feels physically weighted down (without physical energy) more than half the time.</td>
</tr>
<tr>
<td><strong>3</strong> = Feels physically weighted down (without physical energy) most of the time, several hours per day, several days per week.</td>
</tr>
</tbody>
</table>

**IDS TOTAL SCORE:**

Range: 0-84
Part IV: Montreal Cognitive Assessment (MoCA)

Montreal Cognitive Assessment 7.1
(MoCA)
Administration and Scoring Instructions

The Montreal Cognitive Assessment (MoCA) was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal.

1. **Alternating Trail Making:**

   **Administration:** The examiner instructs the subject: "Please draw a line, going from a number to a letter in ascending order. Begin here [point to (1)] and draw a line from 1 then to A then to 2 and so on. End here [point to (E)]."

   **Scoring:** Allocate one point if the subject successfully draws the following pattern: 1 –A- 2- B- 3- C- 4- D- 5- E, without drawing any lines that cross. Any error that is not immediately self-corrected earns a score of 0.

2. **Visuoconstructional Skills (Cube):**

   **Administration:** The examiner gives the following instructions, pointing to the cube: “Copy this drawing as accurately as you can, in the space below”.

   **Scoring:** One point is allocated for a correctly executed drawing.
   - Drawing must be three-dimensional
   - All lines are drawn
   - No line is added
   - Lines are relatively parallel and their length is similar (rectangular prisms are accepted)

   A point is not assigned if any of the above-criteria are not met.

3. **Visuoconstructional Skills (Clock):**

   **Administration:** Indicate the right third of the space and give the following instructions: “Draw a clock. Put in all the numbers and set the time to 10 past 11”.

   **Scoring:** One point is allocated for each of the following three criteria:
   - Contour (1 pt.): the clock face must be a circle with only minor distortion acceptable (e.g., slight imperfection on closing the circle);
   - Numbers (1 pt.): all clock numbers must be present with no additional numbers; numbers must be in the correct order and placed in the approximate quadrants on the
clock face; Roman numerals are acceptable; numbers can be placed outside the circle contour;
• Hands (1 pt.): there must be two hands jointly indicating the correct time; the hour hand must be clearly shorter than the minute hand; hands must be centred within the clock face with their junction close to the clock centre.

A point is not assigned for a given element if any of the above-criteria are not met.

4. **Naming:**

Administration: Beginning on the left, point to each figure and say: “Tell me the name of this animal”.

Scoring: One point each is given for the following responses: (1) lion (2) rhinoceros or rhino (3) camel or dromedary.

5. **Memory:**

Administration: The examiner reads a list of 5 words at a rate of one per second, giving the following instructions: “This is a memory test. I am going to read a list of words that you will have to remember now and later on. Listen carefully. When I am through, tell me as many words as you can remember. It doesn’t matter in what order you say them”. Mark a check in the allocated space for each word the subject produces on this first trial. When the subject indicates that (s)he has finished (has recalled all words), or can recall no more words, read the list a second time with the following instructions: “I am going to read the same list for a second time. Try to remember and tell me as many words as you can, including words you said the first time.” Put a check in the allocated space for each word the subject recalls after the second trial.

At the end of the second trial, inform the subject that (s)he will be asked to recall these words again by saying, “I will ask you to recall those words again at the end of the test.”

Scoring: No points are given for Trials One and Two.

6. **Attention:**

Forward Digit Span: Administration: Give the following instruction: “I am going to say some numbers and when I am through, repeat them to me exactly as I said them”. Read the five number sequence at a rate of one digit per second.

Backward Digit Span: Administration: Give the following instruction: “Now I am going to say some more numbers, but when I am through you must repeat them to me in the backwards order.” Read the three number sequence at a rate of one digit per second.
Scoring: Allocate one point for each sequence correctly repeated, *(N.B.: the correct response for the backwards trial is 2-4-7)*.

**Vigilance:** Administration: The examiner reads the list of letters at a rate of one per second, after giving the following instruction: “*I am going to read a sequence of letters. Every time I say the letter A, tap your hand once. If I say a different letter, do not tap your hand*.”

Scoring: Give one point if there is zero to one errors (an error is a tap on a wrong letter or a failure to tap on letter A).

**Serial 7s:** Administration: The examiner gives the following instruction: “*Now, I will ask you to count by subtracting seven from 100, and then, keep subtracting seven from your answer until I tell you to stop.*” Give this instruction twice if necessary.

Scoring: This item is scored out of 3 points. Give no (0) points for no correct subtractions, 1 point for one correction subtraction, 2 points for two-to-three correct subtractions, and 3 points if the participant successfully makes four or five correct subtractions. Count each correct subtraction of 7 beginning at 100. Each subtraction is evaluated independently; that is, if the participant responds with an incorrect number but continues to correctly subtract 7 from it, give a point for each correct subtraction. For example, a participant may respond “92 – 85 – 78 – 71 – 64” where the “92” is incorrect, but all subsequent numbers are subtracted correctly. This is one error and the item would be given a score of 3.

7. **Sentence repetition:**

Administration: The examiner gives the following instructions: “*I am going to read you a sentence. Repeat it after me, exactly as I say it [pause]: I only know that John is the one to help today.*” Following the response, say: “*Now I am going to read you another sentence. Repeat it after me, exactly as I say it [pause]: The cat always hid under the couch when dogs were in the room.*”

Scoring: Allocate 1 point for each sentence correctly repeated. Repetition must be exact. Be alert for errors that are omissions (e.g., omitting "only", "always") and substitutions/additions (e.g., "John is the one who helped today;" substituting "hides" for "hid", altering plurals, etc.).

8. **Verbal fluency:**

Administration: The examiner gives the following instruction: “*Tell me as many words as you can think of that begin with a certain letter of the alphabet that I will tell you in a moment. You can say any kind of word you want, except for proper nouns (like Bob or Boston), numbers, or words that begin with the same sound but have a different suffix,*"
for example, love, lover, loving. I will tell you to stop after one minute. Are you ready? [Pause] Now, tell me as many words as you can think of that begin with the letter F. [time for 60 sec]. Stop.”

Scoring: Allocate one point if the subject generates 11 words or more in 60 sec. Record the subject’s response in the bottom or side margins.

9. **Abstraction:**

Administration: The examiner asks the subject to explain what each pair of words has in common, starting with the example: “Tell me how an orange and a banana are alike”. If the subject answers in a concrete manner, then say only one additional time: “Tell me another way in which those items are alike”. Do not give any additional instructions or clarification. After the practice trial, say: “Now, tell me how a train and a bicycle are alike”. Following the response, administer the second trial, saying: “Now tell me how a ruler and a watch are alike”. Do not give any additional instructions or prompts.

Scoring: Only the last two item pairs are scored. Give 1 point to each item pair correctly answered. The following responses are acceptable:

- Train-bicycle = means of transportation, means of travelling, you take trips in both;
- Ruler-watch = measuring instruments, used to measure.

The following responses are not acceptable: Train-bicycle = they have wheels;
- Ruler-watch = they have numbers.

10. **Delayed recall:**

Administration: The examiner gives the following instruction: “I read some words to you earlier, which I asked you to remember. Tell me as many of those words as you can remember.” Make a check mark (✓) for each of the words correctly recalled spontaneously without any cues, in the allocated space.

**Scoring:** Allocate 1 point for each word recalled freely without any cues.

**Optional:**

Following the delayed free recall trial, prompt the subject with the semantic category cue provided below for any word not recalled. Make a check mark (✓) in the allocated space if the subject remembered the word with the help of a category or multiple-choice cue. Prompt all non-recalled words in this manner. If the subject does not recall the word after the category cue, give him/her a multiple choice trial, using the following example instruction, “Which of the following words do you think it was, NOSE, FACE, or HAND?”

Use the following category and/or multiple-choice cues for each word, when appropriate:

<table>
<thead>
<tr>
<th>FACE:</th>
<th>category cue: part of the body</th>
<th>multiple choice: nose, face, hand</th>
</tr>
</thead>
<tbody>
<tr>
<td>VELVET:</td>
<td>category cue: type of fabric</td>
<td>multiple choice: denim, cotton, velvet</td>
</tr>
</tbody>
</table>
### Scoring

**No points are allocated for words recalled with a cue.** A cue is used for clinical information purposes only and can give the test interpreter additional information about the type of memory disorder. For memory deficits due to retrieval failures, performance can be improved with a cue. For memory deficits due to encoding failures, performance does not improve with a cue.

### 11. Orientation:

**Administration:** The examiner gives the following instructions: “Tell me the date today”. If the subject does not give a complete answer, then prompt accordingly by saying: “Tell me the [year, month, exact date, and day of the week].” Then say: “Now, tell me the name of this place, and which city it is in.”

**Scoring:** Give one point for each item correctly answered. The subject must tell the exact date and the exact place (name of hospital, clinic, office). No points are allocated if subject makes an error of one day for the day and date.

**TOTAL SCORE:** Sum all subscores listed on the right-hand side. Add one point for an individual who has 12 years or fewer of formal education, for a possible maximum of 30 points. A final total score of 26 and above is considered normal.
MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME: ____________________________  Date of birth: ____________  Sex: ____________  DATE: ____________

VISUOSPATIAL / EXECUTIVE

Copy cube

Draw CLOCK (Ten past eleven) (3 points)

POINTS

NAME:

MEMORY
Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

FACE
VELVET
CHURCH
DAISY
RED

1st trial
2nd trial

No points

ATTENTION

Read list of digits (1 digit/sec.). Subject has to repeat them in the forward order

Subject has to repeat them in the backward order

No points if ≥ 2 errors

Points for correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt

LANGUAGE

Repeat: I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] (≥ 11 words)

ABstraction

Similarity between e.g. banana - orange = fruit [ ] train - bicycle [ ] watch - ruler [ ]

Points for uncued recall only

DELAYED RECALL

Optional

ORIENTATION

[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

POINTS

TOTAL

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Administered by: ____________________________  Normal: ≥ 26 / 30

Add 1 point if ≤ 12 yr. ed.
Montreal Cognitive Assessment (MoCA)  
Version 2

Administration and Scoring Instructions

The Montreal Cognitive Assessment (MoCA) was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal.

1. Alternating Trail Making:

Administration: The examiner instructs the subject: "Please draw a line, going from a number to a letter in ascending order. Begin here [point to (1)] and draw a line from 1 then to A then to 2 and so on. End here [point to (E)]."

Scoring: Allocate one point if the subject successfully draws the following pattern:
1 − A − 2 − B − 3 − C − 4 − D − 5 − E, without drawing any lines that cross. Any error that is not immediately self-corrected earns a score of 0.

2. Visuoconstructional Skills (Rectangle):

Administration: The examiner gives the following instructions, pointing to the rectangle: “Copy this drawing as accurately as you can, in the space below”.

Scoring: One point is allocated for a correctly executed drawing.
- Drawing must be three-dimensional
- All lines are drawn
- No line is added
- The horizontal lines are relatively parallel.
- The object must be clearly rectangular (i.e., the shorter vertical sides cannot be more than ¾ of the length of the longer horizontal lines.

A point is not assigned if any of the above-criteria are not met.

3. Visuoconstructional Skills (Clock):

Administration: Indicate the right third of the space and give the following instructions: “Draw a clock. Put in all the numbers and set the time to 5 past 4”.

Scoring: One point is allocated for each of the following three criteria:
- Contour (1 pt.): the clock face must be a circle with only minor distortion acceptable (e.g., slight imperfection on closing the circle);
- Numbers (1 pt.): all clock numbers must be present with no additional numbers; numbers must be in the correct order and placed in the approximate quadrants on the clock face; Roman numerals are acceptable; numbers can be placed outside the circle contour;
• Hands (1 pt.): there must be two hands jointly indicating the correct time; the hour hand must be clearly shorter than the minute hand; hands must be centred within the clock face with their junction close to the clock centre.

A point is not assigned for a given element if any of the above-criteria are not met.

4. Naming:

Administration: Beginning on the left, point to each figure and say: “Tell me the name of this animal”.

Scoring: One point each is given for the following responses: (1) giraffe; (2) bear (or specific varieties of bears); (3) hippopotamus (or hippo).

5. Memory:

Administration: The examiner reads a list of 5 words at a rate of one per second, giving the following instructions:

“This is a memory test. I am going to read a list of words that you will have to remember now and later on. Listen carefully. When I am through, tell me as many words as you can remember. It doesn’t matter in what order you say them.”

Mark a check in the allocated space for each word the subject produces on this first trial. When the subject indicates that (s)he has finished (has recalled all words), or can recall no more words, read the list a second time with the following instructions:

“I am going to read the same list for a second time. Try to remember and tell me as many words as you can, including words you said the first time.”

Put a check in the allocated space for each word the subject recalls after the second trial. At the end of the second trial, inform the subject that (s)he will be asked to recall these words again by saying,

“I will ask you to recall those words again at the end of the test.”

Scoring: No points are given for Trials One and Two. Scoring is based on the delayed recall trial.

6. Attention:

Forward Digit Span: Administration: Give the following instruction: “I am going to say some numbers and when I am through, repeat them to me exactly as I said them”. Read the five number sequence at a rate of one digit per second.

Backward Digit Span: Administration: Give the following instruction: “Now I am going to say some more numbers, but when I am through you must repeat them to me in the backwards order.” Read the three number sequence at a rate of one digit per second.
Scoring: Allocate one point for each sequence correctly repeated, (N.B.: the correct response for the backwards trial is 2-5-8).

Vigilance: Administration: The examiner reads the list of letters at a rate of one per second, after giving the following instruction: “I am going to read a sequence of letters. Every time I say the letter A, tap your hand once. If I say a different letter, do not tap your hand”.

Scoring: Give one point if there is zero to one errors (an error is a tap on a wrong letter or a failure to tap on letter A).

Serial 7s: Administration: The examiner gives the following instruction: “Now, I will ask you to count by subtracting 7 from 90, and then, keep subtracting 7 from your answer until I tell you to stop.” Give this instruction twice if necessary.

Scoring: This item is scored out of 3 points. Give no (0) points for no correct subtractions, 1 point for one correction subtraction, 2 points for two-to-three correct subtractions, and 3 points if the participant successfully makes four or five correct subtractions. Count each correct subtraction of 7 beginning at 100. Each subtraction is evaluated independently; that is, if the participant responds with an incorrect number but continues to correctly subtract 7 from it, give a point for each correct subtraction. For example, a participant may respond “82 – 75 – 68 – 61” where the “82” is incorrect, but all subsequent numbers are subtracted correctly. This is one error and the item would be given a score of 3.

7. Sentence repetition:

Administration: The examiner gives the following instructions: “I am going to read you a sentence. Repeat it after me, exactly as I say it [pause]: A bird can fly into closed windows if it’s dark and windy.”

Following the response, say: “Now I am going to read you another sentence. Repeat it after me, exactly as I say it [pause]: The caring grandmother sent groceries over a week ago.”

Scoring: Allocate 1 point for each sentence correctly repeated. Repetition must be exact. Be alert for errors that are omissions (e.g., omitting "easily", "over") and substitutions/additions (e.g., "Birds can easily fly into closed windows . . ."); substituting "stormy" for "windy", altering plurals, etc.).

8. Verbal fluency:

Administration: The examiner gives the following instruction: “Tell me as many words as you can think of that begin with a certain letter of the alphabet that I will tell you in a moment. You can say any kind of word you want, except for proper nouns (like Bob or Boston), numbers, or words that begin with the same sound but have a different suffix, for example, love, lover, loving. I will tell you to stop after one minute. Are you ready? [Pause] Now, tell me as many words as you can think of that begin with the letter S. [time for 60 sec]. Stop.”
Scoring: Allocate one point if the subject generates 11 words or more in 60 sec. Record the subject’s response in the bottom or side margins.

9. Abstraction:

Administration: The examiner asks the subject to explain what each pair of words has in common, starting with the example: “Tell me how a carrot and a potato are alike”. If the subject answers in a concrete manner, then say only one additional time: “Tell me another way in which those items are alike”. If the subject does not give the appropriate response (vegetable), say, “Yes, and they are also both vegetable”. Do not give any additional instructions or clarification.

After the practice trial, say: “Now, tell me how a diamond and a ruby are alike”.
Following the response, administer the second trial, saying: “Now tell me how a cannon and a rifle are alike”. Do not give any additional instructions or prompts.

Scoring: Only the last two item pairs are scored. Give 1 point to each item pair correctly answered. The following responses are acceptable:
diamond-ruby = gem stones, precious stones, jewels; cannon-rifle = weapons, guns, used for hurting/killing people, used in war.

The following responses are not acceptable:
diamond-ruby = from the earth cannon-rifle: fires/shoots; ammunition

10. Delayed recall:

Administration: The examiner gives the following instruction: “I read some words to you earlier, which I asked you to remember. Tell me as many of those words as you can remember.”

Make a check mark (✓) for each of the words correctly recalled spontaneously without any cues, in the allocated space.
**Scoring:** Allocate 1 point for each word recalled freely *without any cues.*

**Optional:**
Following the delayed free recall trial, prompt the subject with the semantic category cue provided below for any word not recalled. Make a check mark (✓) in the allocated space if the subject remembered the word with the help of a category or multiple-choice cue. Prompt all non-recalled words in this manner. If the subject does not recall the word after the category cue, give him/her a multiple choice trial, using the following example instruction, *“Which of the following words do you think it was, CAR, TRUCK, or PLANE?”*

Use the following category and/or multiple-choice cues for each word, when appropriate:

<table>
<thead>
<tr>
<th>Word</th>
<th>Category Cue</th>
<th>Multiple Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRUCK</td>
<td>mode of transportation</td>
<td>car, truck, plane</td>
</tr>
<tr>
<td>BANANA</td>
<td>type of fruit</td>
<td>pear, apple, banana</td>
</tr>
<tr>
<td>VIOLIN</td>
<td>type of musical instrument</td>
<td>violin, harp, guitar</td>
</tr>
<tr>
<td>DESK</td>
<td>type of furniture</td>
<td>chair, desk, bed</td>
</tr>
<tr>
<td>GREEN</td>
<td>a colour</td>
<td>green, yellow, black</td>
</tr>
</tbody>
</table>

**Scoring:** No points are allocated for words recalled with a cue. A cue is used for clinical information purposes only and can give the test interpreter additional information about the type of memory disorder. For memory deficits due to retrieval failures, performance can be improved with a cue. For memory deficits due to encoding failures, performance does not improve with a cue.

11. **Orientation:**
Administration: The examiner gives the following instructions: “Tell me the date today”. If the subject does not give a complete answer, then prompt accordingly by saying: “Tell me the [year, month, exact date, and day of the week].” Then say: “Now, tell me the name of this place, and which city it is in.”

Scoring: Give one point for each item correctly answered. The subject must tell the exact date and the exact place (name of hospital, clinic, office). No points are allocated if subject makes an error of one day for the day and date.

**TOTAL SCORE:** Sum all subscores listed on the right-hand side. Add one point for an individual who has 12 years or fewer of formal education, for a possible maximum of 30 points. A final total score of 26 and above is considered normal.
Montreal Cognitive Assessment (MoCA)
Version 3

Administration and Scoring Instructions

The Montreal Cognitive Assessment (MoCA) was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal.

1. **Alternating Trail Making:**

   **Administration:** The examiner instructs the subject: "Please draw a line, going from a number to a letter in ascending order. Begin here [point to (1)] and draw a line from 1 then to A then to 2 and so on. End here [point to (E)]."

   **Scoring:** Allocate one point if the subject successfully draws the following pattern:
   - 1 – A - 2 - B - 3 - C - 4 - D - 5 - E, without drawing any lines that cross.
   Any error that is not immediately self-corrected earns a score of 0.

2. **Visuoconstructional Skills (Cylinder):**

   **Administration:** The examiner gives the following instructions, pointing to the cylinder: “Copy this drawing as accurately as you can, in the space below”.

   **Scoring:** One point is allocated for a correctly executed drawing.
   - Drawing must be three-dimensional
   - All lines/ovals are drawn
   - No line is added
   - The horizontal lines are relatively parallel.
   - The objects at the end must be ovals rather than circles.
   - The horizontal lines must touch the top/bottom of the ovals.
A point is not assigned if any of the above-criteria are not met.

3. **Visuoconstructional Skills (Clock):**

**Administration:** Indicate the right third of the space and give the following instructions: “Draw a clock. Put in all the numbers and set the time to ten past nine”.

**Scoring:** One point is allocated for each of the following three criteria:
- Contour (1 pt.): the clock face must be a circle with only minor distortion acceptable (e.g., slight imperfection on closing the circle);
- Numbers (1 pt.): all clock numbers must be present with no additional numbers; numbers must be in the correct order and placed in the approximate quadrants on the clock face; Roman numerals are acceptable; numbers can be placed outside the circle contour;
- Hands (1 pt.): there must be two hands jointly indicating the correct time; the hour hand must be clearly shorter than the minute hand; hands must be centred within the clock face with their junction close to the clock centre.

A point is not assigned for a given element if any of the above-criteria are not met.

4. **Naming:**

**Administration:** Beginning on the left, point to each figure and say: “Tell me the name of this animal”.

**Scoring:** One point each is given for the following responses: (1) donkey (or mule); (2) pig (or hog); (3) kangaroo.

5. **Memory:**

**Administration:** The examiner reads a list of 5 words at a rate of one per second, giving the following instructions: “This is a memory test. I am going to read a list of words that you will have to remember now and later on. Listen carefully. When I am
through, tell me as many words as you can remember. It doesn’t matter in what order you say them.”

Mark a check in the allocated space for each word the subject produces on this first trial. When the subject indicates that (s)he has finished (has recalled all words), or can recall no more words, read the list a second time with the following instructions: “I am going to read the same list for a second time. Try to remember and tell me as many words as you can, including words you said the first time.”

Put a check in the allocated space for each word the subject recalls after the second trial. At the end of the second trial, inform the subject that (s)he will be asked to recall these words again by saying, “I will ask you to recall those words again at the end of the test.”

Scoring: No points are given for Trials One and Two. Scoring is based on the delayed recall trial.

6. **Attention:**

   **Forward Digit Span: Administration:** Give the following instruction: “I am going to say some numbers and when I am through, repeat them to me exactly as I said them”. Read the five number sequence at a rate of one digit per second.

   **Backward Digit Span: Administration:** Give the following instruction: “Now I am going to say some more numbers, but when I am through you must repeat them to me in the backwards order.” Read the three number sequence at a rate of one digit per second.

   Scoring: Allocate one point for each sequence correctly repeated, (N.B.: the correct response for the backwards trial is 4-7-1).

7. **Vigilance:**

   **Administration:** The examiner reads the list of letters at a rate of one per second, after giving the following instruction: “I am going to read a sequence of letters. Every time I say the letter A, tap your hand once. If I say a different letter, do not tap your hand”.

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Scoring: Give one point if there is zero to one errors (an error is a tap on a wrong letter or a failure to tap on letter A).

8. **Serial 7s:**

Administration: The examiner gives the following instruction: “Now, I will ask you to count by subtracting 7 from 80, and then, keep subtracting 7 from your answer until I tell you to stop.” Give this instruction twice if necessary.

Scoring: This item is scored out of 3 points. Give no (0) points for no correct subtractions, 1 point for one correction subtraction, 2 points for two-to-three correct subtractions, and 3 points if the participant successfully makes four or five correct subtractions. Count each correct subtraction of 7 beginning at 80. Each subtraction is evaluated independently; that is, if the participant responds with an incorrect number but continues to correctly subtract 7 from it, give a point for each correct subtraction. For example, a participant may respond “72 – 65 – 58 – 51 – 44” where the “72” is incorrect, but all subsequent numbers are subtracted correctly. This is one error and the item would be given a score of 3.

9. **Sentence repetition:**

Administration: The examiner gives the following instructions: “I am going to read you a sentence. Repeat it after me, exactly as I say it [pause]: She heard his lawyer was the one to sue after the accident.”

Following the response, say: “Now I am going to read you another sentence. Repeat it after me, exactly as I say it [pause]: The little girls who were given too much candy got stomach aches.”

Scoring: Allocate 1 point for each sentence correctly repeated. Repetition must be exact. Be alert for errors that are omissions (e.g., omitting “too much”) and substitutions/additions (e.g., ” . . . his lawyer sued after . . .”; “the girls”), altering plurals, etc.

10. **Verbal fluency:**

Administration: The examiner gives the following instruction: “Tell me as many words as you can think of that begin with a certain letter of the alphabet that I will tell you in a moment. You can say any kind of word you want, except
for proper nouns (like Peter or Paris), numbers, or words that begin with the same sound but have a different suffix, for example, love, lover, loving. I will tell you to stop after one minute. Are you ready? [Pause] Now, tell me as many words as you can think of that begin with the letter B. [time for 60 sec]. Stop.”

**Scoring:** Allocate one point if the subject generates 11 words or more in 60 sec. Record the subject’s response in the bottom or side margins.

11. **Abstraction:**

**Administration:** The examiner asks the subject to explain what each pair of words has in common, starting with the example: “Tell me how an orange and a banana are alike”. If the subject answers in a concrete manner, then say only one additional time: “Tell me another way in which those items are alike”. If the subject does not give the appropriate response (fruit), say, “Yes, and they are also both fruit.” Do not give any additional instructions or clarification. After the practice trial, say: “Now, tell me how an eye and an ear are alike”.

Following the response, administer the second trial, saying: “Now tell me how a trumpet and a piano are alike”. Do not give any additional instructions or prompts.

**Scoring:** Only the last two item pairs are scored. Give 1 point to each item pair correctly answered. The following responses are acceptable: eye-ear = sensory organs, parts of the head, parts of the body; trumpet-piano = musical instruments, you can play them.

The following responses are not acceptable:

- eye-ear = parts of the face.

12. **Delayed recall:**

**Administration:** The examiner gives the following instruction: “I read some words to you earlier, which I asked you to remember. Tell me as many of those words as you can remember.”

Make a check mark (✓) for each of the words correctly recalled spontaneously without any cues, in the allocated space.

**Scoring:** Allocate 1 point for each word recalled freely **without any cues.**
Optional:

Following the delayed free recall trial, prompt the subject with the semantic category cue provided below for any word not recalled. Make a check mark (✓) in the allocated space if the subject remembered the word with the help of a category or multiple-choice cue. Prompt all non-recalled words in this manner. If the subject does not recall the word after the category cue, give him/her a multiple choice trial, using the following example instruction, “Which of the following words do you think it was, BICYCLE, TRAIN, or BOAT?”

Use the following category and/or multiple-choice cues for each word, when appropriate:

<table>
<thead>
<tr>
<th>Category</th>
<th>Category Cue</th>
<th>Multiple Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRAIN</td>
<td>mode of transportation</td>
<td>bicycle, train, boat</td>
</tr>
<tr>
<td>EGG</td>
<td>something you eat</td>
<td>sandwich, carrot, egg</td>
</tr>
<tr>
<td>HAT</td>
<td>article of clothing</td>
<td>hat, glove, scarf</td>
</tr>
<tr>
<td>CHAIR</td>
<td>piece of furniture</td>
<td>table, chair, lamp</td>
</tr>
<tr>
<td>BLUE</td>
<td>a colour</td>
<td>blue, brown, orange</td>
</tr>
</tbody>
</table>

Scoring: No points are allocated for words recalled with a cue. A cue is used for clinical information purposes only and can give the test interpreter additional information about the type of memory disorder. For memory deficits due to retrieval failures, performance can be improved with a cue. For memory deficits due to encoding failures, performance does not improve with a cue.
13. **Orientation:**

**Administration:** The examiner gives the following instructions: “Tell me the date today”. If the subject does not give a complete answer, then prompt accordingly by saying: “Tell me the [year, month, exact date, and day of the week].” Then say: “Now, tell me the name of this place, and which city it is in.”

**Scoring:** Give one point for each item correctly answered. The subject must tell the exact date and the exact place (name of hospital, clinic, office). No points are allocated if subject makes an error of one day for the day and date.

**TOTAL SCORE:** Sum all subscores listed on the right-hand side. Add one point for an individual who has 12 years or fewer of formal education, for a possible maximum of 30 points. A final total score of 26 and above is considered normal.
Part V: Patient-Reported Outcomes Measurement Information System—Anxiety Short Form (PROMIS 8A)

<table>
<thead>
<tr>
<th>Investigating Cognitive/Affective/Sleep Symptoms in Patients Receiving High-Dose Interleukin-2 Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROMIS Emotional Distress—Anxiety—Short Form 8a</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient Number: ___ ___ ___</th>
<th>Hospital Admission: ___</th>
<th>Baseline: Y/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Initials: ___ ___ ___</td>
<td>Date: ___ / ___ / ____</td>
<td>Doses Completed: ___</td>
</tr>
</tbody>
</table>

Please respond to each question or statement by marking one box per row.

In the past 7 days...

1. I felt fearful

<table>
<thead>
<tr>
<th>1. I felt fearful</th>
<th>Never ___</th>
<th>Rarely ___</th>
<th>Sometimes ___</th>
<th>Often ___</th>
<th>Always ___</th>
</tr>
</thead>
</table>

2. I found it hard to focus on anything other than my anxiety

<table>
<thead>
<tr>
<th>2. I found it hard to focus on anything other than my anxiety</th>
<th>Never ___</th>
<th>Rarely ___</th>
<th>Sometimes ___</th>
<th>Often ___</th>
<th>Always ___</th>
</tr>
</thead>
</table>

3. My worries overwhelmed me

<table>
<thead>
<tr>
<th>3. My worries overwhelmed me</th>
<th>Never ___</th>
<th>Rarely ___</th>
<th>Sometimes ___</th>
<th>Often ___</th>
<th>Always ___</th>
</tr>
</thead>
</table>

4. I felt uneasy

<table>
<thead>
<tr>
<th>4. I felt uneasy</th>
<th>Never ___</th>
<th>Rarely ___</th>
<th>Sometimes ___</th>
<th>Often ___</th>
<th>Always ___</th>
</tr>
</thead>
</table>

5. I felt nervous

<table>
<thead>
<tr>
<th>5. I felt nervous</th>
<th>Never ___</th>
<th>Rarely ___</th>
<th>Sometimes ___</th>
<th>Often ___</th>
<th>Always ___</th>
</tr>
</thead>
</table>

6. I felt like I needed help for my anxiety

<table>
<thead>
<tr>
<th>6. I felt like I needed help for my anxiety</th>
<th>Never ___</th>
<th>Rarely ___</th>
<th>Sometimes ___</th>
<th>Often ___</th>
<th>Always ___</th>
</tr>
</thead>
</table>

7. I felt anxious

<table>
<thead>
<tr>
<th>7. I felt anxious</th>
<th>Never ___</th>
<th>Rarely ___</th>
<th>Sometimes ___</th>
<th>Often ___</th>
<th>Always ___</th>
</tr>
</thead>
</table>

8. I felt tense

<table>
<thead>
<tr>
<th>8. I felt tense</th>
<th>Never ___</th>
<th>Rarely ___</th>
<th>Sometimes ___</th>
<th>Often ___</th>
<th>Always ___</th>
</tr>
</thead>
</table>
Part VI: Patient-Reported Outcomes Measurement Information System - Depression Short Form (PROMIS 8B)

<table>
<thead>
<tr>
<th>Investigating Cognitive/Affective/Sleep Symptoms in Patients Receiving High-Dose Interleukin-2 Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROMIS Emotional Distress--Depression--Short Form 8b</td>
</tr>
<tr>
<td>Patient Number: __   ___   ___</td>
</tr>
<tr>
<td>Patient Initials: __   ___   ___</td>
</tr>
</tbody>
</table>

Please respond to each question or statement by marking one box per row.

In the past 7 days...

<table>
<thead>
<tr>
<th>Question</th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I felt worthless</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>2. I felt that I had nothing to look forward to</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>3. I felt helpless</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>4. I felt sad</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>5. I felt like a failure</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>6. I felt depressed</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>7. I felt unhappy</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td>8. I felt hopeless</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
</tbody>
</table>
Appendix C: Semi-Structured Interviews

Part I: Patient Semi-Structured Interview Template

IL-2 Patient Exit Interview:
I want to thank you today for taking the time to speak with me today. I want to learn about you and your experience with high-dose Interleukin-2. Our interview will take approximately 30 minutes. You will be recorded so that I do not miss valuable information. I will also be taking notes so that I am able to follow-up with any questions that may be unclear.

Initial Open-Ended Questions:
- Can you tell me when you were admitted for IL-2 therapy?
- Can you tell me a little bit about your hospital experience related to your treatment?
- Can you describe your level of familiarity with Interleukin-2 therapy prior to your admission for treatment?
- Can you tell me how many doses of IL-2 you received?

Intermediate Questions:
- Can you describe some of the cognitive, affective or sleep changes you experienced?
  - When did this symptom first appear?
  - How long did it last?
  - How severe was this symptom? Explain the situation.
  - Did anything make it better?
  - Did anything make it worse?
- Can you describe your relationship with your care partner? What was his/her role during your hospitalization?
  - Can you explain the pros of having a care partner at the bedside?
  - Can you explain the cons?
- During the time when you completed the four scales, you mentioned that you experienced _______. Can you please describe the context, and situation?
  - Have you ever experienced ______ before?
- Can you describe what exacerbated the situation? Lessened the situation?
  - Which alteration would you classify as most severe? Why?
  - Which alteration would you classify as least severe? Why?
- Are there any specific alterations you think we need to screen for more thoroughly in future IL-2 patients?
-Were there any patterns in your symptoms that you noticed during IL-2 therapy? If so, what were these patterns?

**Ending Questions:**
-Is there anything that you might not have thought about before that occurred to you during this interview?
-Is there anything you think I need to know?
-What suggestions do you have about how we can best support future patients receiving IL-2 therapy, and their care partners?

Thank you so much for your time today. Please feel free to contact me if there is anything else you would like to discuss.
Part II: Care Partner Semi-Structured Interview Template

Care Partner Exit Interview:
I want to thank you today for taking the time to speak with me today. I understand that you were the care partner caring for Mr./Mrs. _________. I want to learn about you and your experience with high-dose Interleukin-2, as well as your experience caring for this patient. Our interview will take approximately 30 minutes. You will be recorded so that I do not miss valuable information. I will also be taking notes so that I am able to follow-up with any questions that may be unclear.

Initial Open-Ended Questions:
- Can you tell me about your relationship to Mr./Mrs. ________?
- How long have you cared for Mr./Mrs. ________?
- When did you take care of Mr./Mrs. ________?
- Can you tell me a little bit about Mr./Mrs. ________?
- Can you describe your level of familiarity with Interleukin-2 therapy?
- How many doses of IL-2 did he/she receive?

Intermediate Questions:
- Can you describe some of the cognitive, affective or sleep changes you witnessed while you stayed at the bedside during his/her treatment?
  - When did this symptom first appear?
  - How long did it last?
  - How severe was this symptom? Explain the situation.
  - Did anything make it better?
  - Did anything make it worse?
- Can you describe your role as the care partner?
  - Can you explain the benefits of you staying at the bedside during therapy?
  - Can you explain the cons?
- After reviewing the semi-structured journal entries that you completed over the past few days, I saw that the IL-2 patient experienced ________. Can you please describe the context, and situation?
  - What, if anything, did you know about this situation/patient prior to event?
  - Can you describe what exacerbated the situation? Lessened the situation?
  - Can you describe the patient’s appetite?
  - Can you describe the patient’s sleep?
  - Which alteration would you classify as most severe? Why?
-Which alteration would you classify as least severe? Why?
-Are there any specific alterations you think we need to screen for more thoroughly?
-Did the patient return to baseline before the next dose of IL-2, and if not can you explain the symptom pattern?

Ending Questions:
-Is there anything that you might not have thought about before that occurred to you during this interview?
-Is there anything you think I need to know?

Thank you so much for your time today. Please feel free to contact me if there is anything else you would like to discuss.
Part III: Primary Nurse Semi-Structured Interview Template

Primary Nurse Exit Interview:
I want to thank you today for taking the time to speak with me today. I understand that you were the primary nurse caring for Mr./Mrs. __________. I want to learn about you and your experience with high-dose Interleukin-2, as well as your experience caring for this patient. Our interview will take approximately 30 minutes. You will be recorded so that I do not miss valuable information. I will also be taking notes so that I am able to follow-up with any questions that may be unclear.

Initial Open-Ended Questions:
-When did you take care of Mr./Mrs. __________?
-Can you tell me a little bit about Mr./Mrs. __________?
-Can you describe your level of familiarity with Interleukin-2 therapy?
-How many doses of IL-2 did he/she receive?

Intermediate Questions:
-Can you describe some of the cognitive, affective or sleep changes you witnessed or received in shift report?
  -When did this symptom first appear?
  -How long did it last?
  -How severe was this symptom? Explain the situation.
  -Did anything make it better?
  -Did anything make it worse?
-Can you describe the role of the care partner?
  -Can you explain the pros of having a care partner at the bedside?
  -Can you explain the cons?
-After reviewing the semi-structured questionnaires completed by the care partner, I saw that the IL-2 patient experienced ________. Can you please describe the context, and situation?
-What, if anything, did you know about this situation/patient prior to event?
-Can you describe what exacerbated the situation? Lessened the situation?
-Can you describe the patient’s appetite?
-Can you describe the patient’s sleep?
-Which alteration would you classify as most severe? Why?
-Which alteration would you classify as least severe? Why?
-Are there any specific alterations you think we need to screen for more thoroughly?
-Did the patient return to baseline before the next dose of IL-2, and if not can you explain the symptom pattern?

**Ending Questions:**
-Is there anything that you might not have thought about before that occurred to you during this interview?
-Is there anything you think I need to know?

Thank you so much for your time today. Please feel free to contact me if there is anything else you would like to discuss.
Appendix D: Journal Entries

Part I: Care Partner Journal Entry Template

Entry 1:

Please check the boxes of symptom change that you witnessed in the patient receiving IL-2.

☐ Altered language/speech
☐ Decreased concentration
☐ Mental fatigue (somnolence, lethargy, exhaustion)
☐ Confusion (ex. urinating on the floor, pulling out IV lines)
☐ Decreased attention/focus
☐ Decreased short-term memory
☐ Decreased orientation (person, place, time, situation)
☐ Increased depression
☐ Increased anxiety
☐ Mood alterations
☐ Sleep disturbances
☐ Hallucinations
☐ Increased sleep
☐ Decreased sleep
☐ Increased happiness
☐ Increased irritability
For the boxes you checked above, please describe the changes you witnessed. When did the symptom appear? How long did the symptom last?

How severe is the symptom? Can you describe the situation? Did anything make this symptom better or worse?

<table>
<thead>
<tr>
<th>Date: __________</th>
<th>Time: __________</th>
<th>IL-2 dose #: __________</th>
</tr>
</thead>
</table>

If there are other changes in the patient that you feel the team should know about, please feel free to write about these changes as well. Please email Tara Mann, RN, at tara.mann@duke.edu or call her at 919-908-6363 if you have any questions or concerns.

| Date: __________ | Time: __________ | IL-2 dose #: __________ |
Part II: Nurse Journal Entry Template

We are asking you to participate in a research study examining the effects of high dose IL-2 therapy. We are interested in learning about the changes in cognition and behavior that occur in patients receiving high-dose Interleukin-2 therapy. The purpose of the study is to find the best way to document these changes. Your participation is voluntary and will involve your recording information about the patient’s cognitive and affective changes after each dose of IL-2 on the form below.

By completing this form, you are consenting to participate in this study and for the information below to be used for research purposes. No identifiable information about you will be collected in this study. You will be asked to respond to this form after each dose of Interleukin-2. Please date and time your entries and place them in the lock box provided.

Date: ___________ Time: ___________ IL-2 dose #: ___________

Please check the boxes of symptom change that you witnessed in the IL-2 patient.

- [ ] Altered language/speech
- [ ] Decreased concentration
- [ ] Mental fatigue (somnolence, lethargy, exhaustion)
- [ ] Confusion (ex. urinating on the floor, pulling out IV lines)
- [ ] Decreased attention/focus
- [ ] Decreased short-term memory
- [ ] Decreased orientation (person, place, time, situation)
- [ ] Increased depression
- [ ] Increased anxiety
☐ Mood alterations
☐ Sleep disturbances
☐ Hallucinations
☐ Increased sleep
☐ Decreased sleep
☐ Increased happiness
☐ Increased irritability

For the boxes you checked above, please describe the changes you witnessed. When did the symptom appear? How long did the symptom last?

How severe is the symptom? Can you describe the situation? Did anything make this symptom better or worse?

Date: ___________        Time: ___________        IL-2 dose #: ___________

If there are other changes in the patient that you feel the team should know about, please feel free to write about these changes as well. Please email Tara Mann, RN, at tara.mann@duke.edu or call her at 919-908-6363 if you have any questions or concerns.
Please list any PRN medications administered to the patient to manage
cognitive/affective changes such as sleeping agents, antidepressants,
antipsychotics, etc.

<table>
<thead>
<tr>
<th>Ex. Medication:</th>
<th>Dose:</th>
<th>Time:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If you do not witness any alterations, please check below.

___“I did not witness any cognitive or behavior changes in the IL-2 patient
during my time with the patient.”
References


family caregiver involvement and influence throughout cancer treatment decision-making. *Patient Education and Counseling, 100*(11), 2035-2046. doi: 10.1016/j.pec.2017.05.014


http://www.cancer.gov/cancertopics/pdq/treatment/melanoma/HealthProfessional/page9


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Biography

Tara Kaur Mann was born on February 1, 1989, in Merritt Island, Florida. She attended Emory University in Atlanta, GA, for her Bachelor of Science in Nursing, graduating in 2011. While a collegiate athlete on the Women’s Crew team, as well as a nursing student, Tara became involved in an Honors Research Program through the Emory University Nell Hodgson Woodruff School of Nursing. During the program, Tara was a member of a research team investigating the effects of high-dose IL-2 in the melanoma population, and gained experience working on an NIH-funded research study.

After graduation, Tara continued participating in research while also acquiring clinical nursing experience working on a medical-oncology floor at Emory Healthcare where she gained first-hand experience seeing the disconnect between research and clinical practice. Tara attended the Duke University School of Nursing where she pursued her Doctorate of Philosophy in Nursing. While studying at Duke University, Tara served as the Student Representative on the PhD Program Committee for two years, and as a member of the Duke Institutional Review Board. She continues to maintain her clinical nursing skills by working on a Bone Marrow Transplant Unit at the University of North Carolina, and maintains a connection to the community through her involvement
in the Cornucopia Cancer Support Group for patients with metastatic disease at the Caring House in Durham, North Carolina.