**PROTOCOL AMENDMENT #__8__**

# LCCC 1726: Randomized Placebo Controlled Trial of High Dose Intravenous Thiamine for the Prevention of Delirium in Allogeneic Hematopoietic Stem Cell Transplantation

**NCT03263442**

**Date Reviewed: 12/30/2020**

**Last Modified: 3/26/2020**

AMENDMENT INCORPORATES (check all that apply):
_X_ Editorial, administrative changes
___ Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

Editorial, administrative changes

(1) The version date was updated throughout the protocol
(2) In Sections 5.8 and 7.5 we have broadened allowable methods of follow-up assessment to include email and online, in addition to in-person assessment, mail, video conferencing, and over the phone. This enhances our ability to complete study assessments and questionnaires whenever possible in cases that in-person assessments (preferred method) are restricted or prohibited.
(3) In Section 7.5 we have modified the follow-up assessment schedule to allow for the three-month follow-up to be completed within four weeks of the specified time point and the six-month follow-up to be completed within 2 months of the specified time point. While we will make every attempt to schedule assessments on their ideal dates, this will allow us more flexibility in scheduling in light of COVID-19 policy.

*Per the PRC Coordinator, this amendment is exempt from PRC review.*

***THE ATTACHED VERSION LAST MODIFIED __3/16/20__ INCORPORATES THE ABOVE REVISIONS***

**April 2017**

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| **PROTOCOL AMENDMENT #__7__** |

**LCCC 1726: Randomized Placebo Controlled Trial of High Dose Intravenous Thiamine for the Prevention of Delirium in Allogeneic Hematopoietic Stem Cell Transplantation**

**AMENDMENT INCORPORATES (check all that apply):**

_X_ Editorial, administrative changes
___ Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

**AMENDMENT RATIONALE AND SUMMARY:**

Editorial, administrative changes

(1) The version date was updated throughout the protocol
(2) We have removed Thomas Shea, MD as a co-investigator given his retirement from UNC.

*Per the PRC Coordinator, this amendment is exempt from PRC review.*

***THE ATTACHED VERSION DATED __1/14/20__ INCORPORATES THE ABOVE REVISIONS***

**April 2017**

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| **PROTOCOL AMENDMENT #__6__** |

**LCCC 1726: Randomized Placebo Controlled Trial of High Dose Intravenous Thiamine for the Prevention of Delirium in Allogeneic Hematopoietic Stem Cell Transplantation**

**AMENDMENT INCORPORATES (check all that apply):**

_X_ Editorial, administrative changes
___ Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

**AMENDMENT RATIONALE AND SUMMARY:**

Editorial, administrative changes

(1) The version date was updated throughout the protocol
(2) In Sections 1.1, 4.1, 5.1, 7.2, and 9.1 we have modified language to expand recruitment to the outpatient setting prior to planned allogeneic bone marrow transplant, in addition to after patients are admitted. This allows us to have additional time to secure formal insurance authorization prior to randomizing participants to our study drug.

*Per the PRC Coordinator, this amendment is exempt from PRC review.*

***THE ATTACHED VERSION DATED __8/13/19__ INCORPORATES THE ABOVE REVISIONS***

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**PROTOCOL AMENDMENT #__5__**

## LCCC 1726: Randomized Placebo Controlled Trial of High Dose Intravenous Thiamine for the Prevention of Delirium in Allogeneic Hematopoietic Stem Cell Transplantation

**AMENDMENT INCORPORATES (check all that apply):**

_X_ Editorial, administrative changes
___ Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

**AMENDMENT RATIONALE AND SUMMARY:**

Editorial, administrative changes

(1) The version date was updated throughout the protocol
(2) In Sections 5.8 and 7.5 we have broadened allowable methods of follow-up assessment to include video conferencing, in addition to in-person assessment, mail, and over the phone.
(3) In Section 7.5 we have modified the follow-up assessment schedule to allow for the six-month follow-up to be completed within 1 month of the specified time point. This enhances our ability to complete assessments in-person (preferred method).

***THE ATTACHED VERSION DATED __1/10/19__ INCORPORATES THE ABOVE REVISIONS***

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**PROTOCOL AMENDMENT #__4__**

# LCCC 1726: Randomized Placebo Controlled Trial of High Dose Intravenous Thiamine for the Prevention of Delirium in Allogeneic Hematopoietic Stem Cell Transplantation

## AMENDMENT INCORPORATES (check all that apply):

_X_ Editorial, administrative changes
_X_ Scientific changes (IRB approval)
_X_ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

## AMENDMENT RATIONALE AND SUMMARY:

Editorial, administrative changes

(1) The version date was updated throughout the protocol
(2) In Sections 5.8 and 7.5 we have broadened allowable methods of follow-up assessment to include mail, in addition to in person assessment and over the phone.
(3) All personnel, except for the Principal Investigator, Co-Investigators, and Biostatistician have been removed from the cover sheet to limit future protocol amendments related only to staff changes, as recommended by the Protocol Review Committee Compliance Coordinator
(4) A minor error in Table 7.1 was corrected. Specifically, in the legend "c." was previously incorrectly attributed to the DRS and "d." to the longitudinal measures.
(5) Throughout the protocol, we have modified the delirium assessment schedule to specify that delirium assessments will be performed at one, three, and six months after transplant for patients who develop delirium in the inpatient phase. This modification was made to ensure that delirium has resolved before completion of longitudinal follow-up measures.
(6) Throughout the protocol, we have modified plan to continue recruitment until we have 60 *evaluable* participants to account for subjects who do not meet criteria for efficacy analysis (as described in Section 7.11) and will subsequently be replaced.

Scientific changes

(1) In Section 7.11 we have modified the requirements for efficacy assessment to stipulate that patients must have delirium assessed at least weekly during hospitalization, until any of the following have occurred: 1.) they develop delirium (primary endpoint); 2.) they are discharged; or 3.) they reach 30 days post-transplant.

Therapy changes

(1) Throughout the protocol, the preparation of our intervention was changed from Thiamine 200 mg diluted in 25 mL 0.9% normal saline to Thiamine 200 mg diluted in 100 mL 0.9% normal saline. Our placebo was changed from 25 mL 0.9% normal saline to 100 mL 0.9% normal saline to maintain blinding. The intervention will be administered over 30 minutes. No changes were made to strength, route (intravenous), frequency (TID), or duration (seven days). This modification was made in response to the nation-wide IV bag shortage following the hurricane in Puerto Rico. This modification in no way increases risk to subjects.

***THE ATTACHED VERSION DATED __9/4/18__ INCORPORATES THE ABOVE REVISIONS***

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**PROTOCOL AMENDMENT #__3__**

# LCCC 1726: Randomized Placebo Controlled Trial of High Dose Intravenous Thiamine for the Prevention of Delirium in Allogeneic Hematopoietic Stem Cell Transplantation

## AMENDMENT INCORPORATES (check all that apply):

_X_ Editorial, administrative changes
_X_ Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

## AMENDMENT RATIONALE AND SUMMARY:

Editorial, administrative changes

(1) The version date was updated throughout the protocol

Scientific changes

(1) Throughout the protocol, we have modified the delirium assessment schedule to acknowledge that there are certain situations, due to an acute medical concern (e.g. intubation, sedation, etc.), in which patients are not evaluable for the purposes of this study and the DRS will not be performed.
(2) In Section 7.11 Assessment of Efficacy we have added the phrase "in evaluable patients" to account for acute medical concerns that prevent participants from being evaluated, as described above.
(3) Throughout the protocol, we have modified the delirium assessment schedule to specify that when patients develop delirium, delirium assessments will be performed daily "when scheduling permits". This allows for greater flexibility for this non-primary outcome (duration of delirium).

***THE ATTACHED VERSION DATED __1/10/18__ INCORPORATES THE ABOVE REVISIONS***

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**PROTOCOL AMENDMENT #__2__**

# LCCC 1726: Randomized Placebo Controlled Trial of High Dose Intravenous Thiamine for the Prevention of Delirium in Allogeneic Hematopoietic Stem Cell Transplantation

## AMENDMENT INCORPORATES (check all that apply):

_X_ Editorial, administrative changes
_X_ Scientific changes (IRB approval)
_X_ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

## AMENDMENT RATIONALE AND SUMMARY:

Editorial, administrative changes

(1) The version date was updated throughout the protocol

Scientific changes

(1) Throughout the protocol, modified schedule of thiamine levels from days 1, 8, 15, 22, and 29 post-transplant to allow for levels to be drawn up to one day earlier or later of this specified schedule. This allows capture of thiamine levels currently missed in patients who are discharged the day before their anticipated next thiamine level lab draw.

Therapy changes

(2) Throughout the protocol, the preparation of our intervention was changed from Thiamine 200 mg diluted in 100 mL 0.9% normal saline to Thiamine 200 mg diluted in 25 mL 0.9% normal saline. Our placebo was changed from 100 mL 0.9% normal saline to 25 mL 0.9% normal saline to maintain blinding. The intervention will be administered over 30 minutes. No changes were made to strength, route (intravenous), frequency (TID), or duration (seven days). This modification was made in response to a severe national shortage of 100 mL bags related to the hurricane in Puerto Rico. This modification in no way increases risk to subjects.

***THE ATTACHED VERSION DATED __11/16/17__ INCORPORATES THE ABOVE REVISIONS***

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**April 2017**

**PROTOCOL AMENDMENT #__1__**

# LCCC 1726: Randomized Placebo Controlled Trial of High Dose Intravenous Thiamine for the Prevention of Delirium in Allogeneic Hematopoietic Stem Cell Transplantation

## AMENDMENT INCORPORATES (check all that apply):

_X_ Editorial, administrative changes
_X_ Scientific changes (IRB approval)
_X_ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

## AMENDMENT RATIONALE AND SUMMARY:

Editorial, administrative changes

(1) The version date was updated throughout the protocol
(2) Stephanie Chien added as the study coordinator
(3) Section 7.9. Samples will be drawn by nurses rather than phlebotomists and stored in McLendon laboratory. This modification in no way increases risk to subjects, but only reflects the actual workflow on the Bone Marrow Transplant Unit.

Scientific changes

(1) Throughout the protocol, Medical/Surgical Tracking Form is omitted, as it was overly inclusive and not necessary to accomplish the study's aims. In its place, a Delirium Risk Factor Form has been added, which will document previous history of delirium, alcohol and substance use, and neurological conditions (stroke, traumatic brain injury, seizures, abnormal brain imaging findings) from chart abstraction.
(2) Throughout the protocol, revised baseline labs to no longer include folate and vitamin B12. These are also not necessary to accomplish the study's aims and not typically drawn on patients undergoing hematopoietic stem cell transplantation (HSCT).
(3) Throughout the protocol, revised schedule of baseline labs (CBC, CMP, Mg, Phos) to within 2 days of transplant, rather than specifically on post-transplant day 1. These labs are routinely drawn on Mondays and Thursdays, so this modification prevents additional blood draws, thereby improving nursing workflow and minimizing patient burden.
(4) Class of concurrent CNS active medications will continue to be documented, but throughout the protocol revised to indicate that details regarding dose, route, frequency, and indication will no longer be captured, as this data will not be necessary to accomplish the study's aims.

(5) The four yes/no questions of the PTSS-14 have been removed, as the results from these four questions are not used in calculating the total score, not typically reported in the literature, and are more appropriate for ICU settings, which the scale was originally designed for. This modification is reflected in Appendix E and does not necessitate modification in other areas of the protocol.

(6) Section 5.2. Language added to explicitly reflect that the PI, primary medical providers, or other emergency personnel may request unblinding of a subject's randomized treatment from the IDS pharmacy.

Therapy changes

(1) Throughout the protocol, the preparation of our intervention was changed from Thiamine 200 mg in a 2 mL syringe to Thiamine 200 mg diluted in 100 mL 0.9% normal saline. Our placebo was changed from 2 mL of 0.9% normal saline to 100 mL 0.9% normal saline to maintain blinding. The intervention will be administered over 30 minutes, rather than the four minutes described in the previous version of this protocol. No changes were made to strength, route (intravenous), frequency (TID), or duration (seven days). This modification was made to improve nursing workflow, as it is not practical for them to administer the syringe by hand at 50 mg/min as outlined in the previous version of the protocol. This modification in no way increases risk to subjects.

**LCCC 1726:**
Randomized Placebo Controlled Trial of High Dose Intravenous Thiamine for the Prevention of Delirium in Allogeneic Hematopoietic Stem Cell Transplantation

**Short Title**: High Dose Intravenous Thiamine for the Prevention of Delirium in Allogeneic Hematopoietic Stem Cell Transplantation

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**Version 9 Date:** 3/16/2020

LCCC 1726:
Randomized Placebo Controlled Trial of High Dose Intravenous Thiamine for the Prevention of Delirium in Allogeneic Hematopoietic Stem Cell Transplantation

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**Signature Page**

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

**Principal Investigator (PI) Name**:____Zev Nakamura M.D._____

**PI Signature:** ___ _____

**Date:**_____3/16/2020_____

**Version date**: 3/16/2020

## TABLE OF CONTENTS

# 1.0 BACKGROUND AND RATIONALE

## 1.1 Study Synopsis

This is a randomized double-blind controlled trial in participants undergoing allogeneic hematopoietic stem cell transplantation (HSCT) to determine if high dose intravenous (IV) thiamine can prevent delirium and minimize the deleterious impact of delirium on health-related quality of life (HRQOL), functional status, and other neuropsychiatric outcomes. We will recruit 60 evaluable patients scheduled for allogeneic HSCT at UNC, randomize them to treatment with high dose IV thiamine (n = 30) versus placebo (n = 30), and systematically evaluate all participants for delirium and related comorbidities. We will use the Delirium Rating Scale (DRS) to measure the severity and duration of delirium immediately prior to transplant and after HSCT until 30 days post-transplant or discharge. We will obtain thiamine levels and other laboratory parameters associated with delirium the day after transplant, and continue to monitor thiamine levels weekly thereafter. We will also monitor HRQOL (FACT-BMT), functional status (ECOG-PS), depression (PROMIS-D), post-traumatic stress symptoms (PTSS-14), and cognitive function (MOCA) prior to transplant and at one, three, and six months after transplant to elucidate the persistent impact of delirium in this population and the potential for thiamine to mitigate these negative outcomes.

## 1.2 Disease Background

Delirium is a highly prevalent and potentially preventable neuropsychiatric condition with major health consequences in cancer patients. Delirium is seen in 25 – 40% of cancer patients,[1,2] and in those with late-stage and terminal cancers the prevalence may be as high as 85%.[3] Delirium is associated with increased length of stay,[4] elevated mortality,[5] impaired activities of daily living,[6] and has profound immediate and long-term impact on mental health with studies demonstrating persistent symptoms of depression,[7] post-traumatic stress,[8] and impaired cognition.[9] Cancer patients undergoing HSCT are at even higher risk given that they typically present with advanced disease and have already received one or more courses of systemic chemotherapy. In the only two studies to evaluate the epidemiology of delirium in HSCT patients, delirium was described in at least 40%, and possibly as many as 73%, of patients during post-transplant hospitalization.[10,11] Delirium in HSCT patients confers worse HRQOL, more severe distress, poor cognitive outcomes, and a 14-fold greater mortality rate.[9,11] In sum, delirium in cancer patients, particularly those receiving HSCT, is extremely common, has major medical and neuropsychiatric consequences that persist even after the delirium has resolved, and, therefore, demands efforts to prevent its occurrence.

Thiamine deficiency is an underappreciated cause of delirium. Wernicke's encephalopathy (WE) is a condition, most commonly but not exclusively associated with alcoholism, in which thiamine deficiency leads to a triad of

clinical signs (ophthalmoplegia, ataxia, and mental status changes). Because its diagnosis requires a high index of suspicion and reliance on complex clinical findings, more than 80% of cases of the closely related Wernicke-Korsakoff Syndrome (WKS) go undiagnosed during patients' lifetimes.[12-14] Of note, WKS refers to the spectrum of neuropsychiatric conditions that result from thiamine deficiency, which includes WE as well as Korsakoff's syndrome, an irreversible dementia with marked anterograde amnesia. Only in the past 20 years have clinicians and researchers become aware of the potential for thiamine deficiency to impact mental status and lead to delirium without the other physical signs of WE.[15] Accordingly, the precise incidence of delirium due to thiamine deficiency is not known. However, this connection, specifically in cancer patients, is rapidly evolving. A recent retrospective study, for example, reported that thiamine deficiency occurred in 55% of cancer patients, 80% of whom demonstrated some mental status abnormality.[16]

HSCT patients are particularly vulnerable to thiamine deficiency. In the only study to systematically monitor thiamine levels in cancer patients undergoing HSCT, 100% of patients developed thiamine deficiency during post-transplant hospitalization.[17] There are several pathways by which HSCT patients become thiamine deficient. First, less thiamine is absorbed from the diet due to anorexia and vomiting common with many cancers and their treatments.[18] Second, there is increased metabolism of thiamine secondary to rapid cell turnover inherent in hematologic malignancies and complications after transplant, such as graft versus host disease (GvHD) and infection. Finally, chemotherapies and calcineurin inhibitors, commonly administered during hospitalization for HSCT, impair conversion of thiamine to its biologically active form.[18,19] There is insufficient data regarding relative incidences of thiamine deficiency or delirium in allogeneic vs. autologous transplants. However, allogeneic transplant recipients do display increased mortality and morbidity, including outcomes such as infection and GvHD, known to increase risk of thiamine deficiency, potentially making them an even greater risk group.[11,20,21] Therefore, while thiamine deficiency is unlikely to be the sole source of delirium in HSCT patients, it appears to be a universal and treatable one.

High dose IV thiamine is a promising intervention for delirium in cancer patients undergoing HSCT. Currently, there is no established way to treat or prevent delirium in this patient population. Standard approaches for delirium management, including use of antipsychotics, are limited by potentially life-threatening side effects in the medically ill. Treatment of suspected thiamine-related mental status changes with high dose IV thiamine, *defined as at least 200 mg three times daily*, has preliminary evidence for improving a variety of cognitive symptoms.[22-25] Unfortunately, delirium due to thiamine deficiency is often missed entirely or diagnosed late in the course of delirium, leading to treatment delays, after patients have been put at risk for immediate and long-term consequences of delirium. This highlights the need for prophylaxis strategies, but surprisingly, the use of high dose IV thiamine has never been studied for the

prevention of delirium in any condition, including in this highly vulnerable HSCT population.

### 1.3 Current Standard of Care

Currently, there is no standard of care for the prevention or treatment of delirium in HSCT patients. There is also no consensus regarding dose for treatment or prophylaxis of delirium specifically due to thiamine deficiency, but it is generally dosed at ≥ 50 mg IV or intramuscularly (IM) daily.[26] An unpublished electronic medical record review from our group, investigating thiamine prescribing practices at UNC Hospitals between 4/4/2014 and 11/1/2015, described over 5,000 prescriptions for thiamine. Of these, 29% (N = 1531) were given IV with 41% (N = 633) of IV prescriptions for doses 200 mg or greater. This same study described 432 subjects who had delirium and received IV thiamine. Only 15 subjects with delirium received at least 200 mg IV three times daily (tid).

### 1.4 High Dose Intravenous Thiamine

For this trial we have chosen to study the effects of high dose IV thiamine. Parenteral thiamine administration has been well studied in large population samples and shown to be safe with the most common adverse effects being immediate, transient burning at the injection site (1.02%) and pruritis (<0.1%).[27-29] Other side effects are sufficiently rare that rates of occurrence are not available.

Thiamine (vitamin B1) is a water soluble vitamin. It is an important cofactor in the Kreb's Cycle and Pentose Phosphate Pathway, thus critical for metabolism of lipids, glucose, amino acids, and neurotransmitters. It is absorbed by an energy-dependent active transport system in the gut, which limits absorption such that no more than 4.5 mg thiamine is absorbed for oral doses 50 mg or greater.[28] It reaches the brain across the blood brain barrier through facilitated diffusion, active transport across the choroid plexus, and simple diffusion mechanisms. Thiamine has FDA indications for Wernicke's encephalopathy and the related Wernicke-Korsakoff syndrome, thiamine deficiency, administration of dextrose-containing fluids, berberi, and peripheral neuritis in pregnancy.[30] It is metabolized in the liver (exact mechanism not known) and excreted in the kidney.

There have not been any studies investigating its use specifically in HSCT patients. The longstanding recommendation for treatment of WE in the United States is 100 mg IV daily. This is based on estimates from experts, developed over 50 years ago, of what might constitute high doses. There have been no clinical studies validating the efficacy of this dosing strategy.[22,23,31] Though the most recent Cochrane review on the subject stated that there was insufficient evidence regarding dose, frequency, route, or duration of thiamine for treatment or prophylaxis of WE and related syndromes,[26] there are currently two sets of guidelines recommending at least 200 mg IV tid from the European Federation of Neurologic Society (EFNS) and Royal College of Physicians (RCP).[28,32] This

dosing strategy has demonstrated efficacy in several case reports.[22-25] The only existing randomized controlled trial investigating the dose response of thiamine on improving mental status abnormalities, revealed that subjects treated with the highest dose studied, 200 mg IM, performed best on one measure of working memory.[33]

### 1.5 Rationale for Clinical Study

Delirium occurs in at least 40%, and up to 73%, of patients undergoing HSCT.[10,11] Delirium is associated with longer length of stay,[4] increased mortality,[5] impaired activities of daily living,[6] and can have profound immediate and long-term effects on mental health with studies demonstrating lasting symptoms of depression,[7] post-traumatic stress,[8] and impaired cognition.[9]

Thiamine deficiency is an underappreciated cause of delirium. Thiamine deficiency has been reported in 100% of patients undergoing HSCT.[17] The co-occurrence of delirium and thiamine deficiency in HSCT is not known, but in cancer patients more broadly thiamine deficiency occurred in 55% of patients, 80% of whom demonstrated some mental status abnormality.[16] There are not sufficient data to support a specific dosing strategy for thiamine repletion to target delirium due to thiamine deficiency in any patient population,[26] and no published studies investigating treatment or prophylaxis of delirium due to thiamine deficiency in HSCT patients.

In this double-blind, randomized controlled trial, we examine the use of high dose IV thiamine to prevent occurrence and decrease severity and duration of delirium. Our study design also allows for additional novel data on the temporal relationship between thiamine deficiency and delirium in HSCT patients.

## 2.0 STUDY OBJECTIVES

### 2.1 Primary Objectives

**2.1.1** To compare delirium incidence between recipients of high dose IV thiamine and placebo during hospitalization for allogeneic HSCT.

### 2.2 Secondary Objectives

**2.2.1** To compare delirium severity between recipients of high dose IV thiamine and placebo during hospitalization for allogeneic HSCT.

**2.2.2** To compare delirium duration between recipients of high dose IV thiamine and placebo during hospitalization for allogeneic HSCT.

**2.2.3** To determine if thiamine status is predictive of subsequent delirium onset.

**2.2.4** To investigate the effects of high dose IV thiamine on long-term health-related quality of life (HRQOL), functional status, depression, post-traumatic stress symptoms, and cognitive functioning in patients who undergo HSCT.

# 3.0 Criteria for Evaluation / Study Endpoints

## 3.1 Primary Endpoint

Delirium incidence will be defined as: DRS > 12. Delirium rating scales will be performed at baseline (prior to transplant) and then three times weekly from day after transplant to 30 days after transplant or discharge, whichever comes first.

## 3.2 Secondary Endpoints

**3.2.1** Delirium duration will be measured in days and delirium severity will be defined as the highest DRS score recorded. If delirium occurs, frequency of assessment will increase to daily, Monday through Friday, as scheduling permits, until delirium resolves.

**3.2.2** We will examine the relationship between thiamine levels at the end of the seven day intervention period and the development of delirium at any point during the post-transplant hospitalization.

**3.2.3** Scores on FACT-BMT, PROMIS-D, PTSS-14, ECOG-PS, and MOCA will be measured at one, three, and six months after transplant.

# 4.0 PATIENT ELIGIBILITY

In order to participate in this study a subject must meet ALL of the eligibility criteria outlined below.

## 4.1 Inclusion Criteria

Eligible subjects must meet all of the following criteria to be enrolled in the study:
**4.1.1** Admission or planned admission to the UNC Hospital Bone Marrow Transplant Unit for allogeneic stem cell transplant.
**4.1.2** At least 18 years of age.
**4.1.3** Able to speak English.
**4.1.4** Able to provide informed consent.

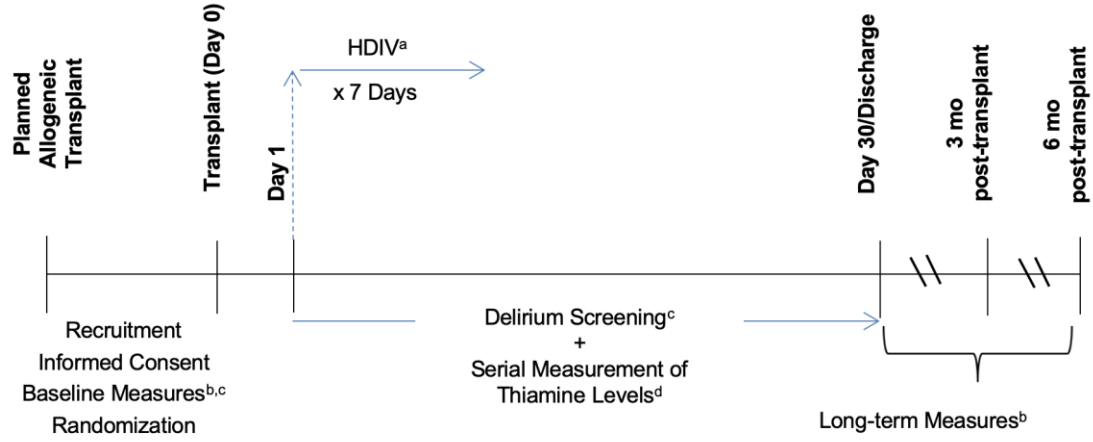
## 4.2 Exclusion Criteria

Eligible subjects must not have any of the following to be enrolled in the study:
**4.2.1** A history of adverse reaction to IV thiamine
**4.2.2** Pregnancy, confirmed by a negative pregnancy test within 30 days of study enrollment

# 5.0 TREATMENT PLAN

## 5.1 Schema

Figure 1: Randomized controlled trial evaluating the efficacy of high dose intravenous thiamine for prevention of delirium in allogeneic hematopoietic stem cell transplantation.




a. High dose IV thiamine in intervention group only (N=30)
b. MOCA, FACT-BMT, PROMIS-D, PTSS-14, ECOG-PS
c. DRS
d. Thiamine levels weekly

## 5.2 Treatment Dosage and Administration

Subjects in the intervention group will receive thiamine 200 mg IV tid for seven days beginning on the day after of transplant. Subjects in the control group will receive 100 mL (equivalent volume to intervention) normal saline IV tid for seven days beginning on the day after transplant. All investigators will be blinded to which patients are assigned to which arm of the study. Only the Investigational Drug Service (IDS) will be aware of which patients will be assigned to which arms. At any time, the PI, primary medical providers, or other emergency personnel may request unblinding of a subject's randomized treatment from IDS. If there is an adverse reaction, subjects will be treated symptomatically and consideration will be given to stopping the medication, as outlined in Section 5.3.

| REGIMEN DESCRIPTION | | | | |
|---|---|---|---|---|
| **Group** | **Agent** | **Dose** | **Route** | **Schedule** |
| Intervention | Thiamine | 200 mg Thiamine HCL solution in 100 mL infusion bag of 0.9% Sodium Chloride | IV over 30 minutes (50 ml/hr) | Post-transplant Days 1 – 7 three times daily |

| | | | | |
|---|---|---|---|---|
| Control | Normal Saline | 100 mL of 0.9% | IV over 30 minutes (50 ml/hr) | Post-transplant Days 1 – 7 three times daily |

**Prescribing Information**
Full prescribing information for thiamine can be found at the following web address: http://editor.fresenius-kabi.us/PIs/Thiamine_Inj_45819E_May_08.pdf

## 5.3 Toxicities and Dosing Delays

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed periodically for the development of any toxicity according to the Time and Events table (Section 7.1). Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0. All severe adverse effects will be evaluated immediately by Drs. Nakamura or Rosenstein and a decision will be made about stopping the study medication.

| **Toxicity and Dosing Delays** | |
|---|---|
| **Event** | **Action** |
| **Anaphylaxis** | |
| Grade 1-2 | N/A |
| Grades 3 – 4 | Stop medication and consider removing subject from trial |
| **Infusion site extravasation** | |
| Grade 1-2 | Hold until AE are tolerable and then restart medication. |
| Grade 3-4 | Withhold until ≤ Grade 2 |
| **Pruritis** | |
| Grade 1 | Will provide topical intervention |
| Grade 2 | Will provide oral intervention (e.g. diphenhydramine) and withhold until < Grade 2 |
| Grade 3 | Will administer oral corticosteroid or immunosuppressive therapy and withhold until < Grade 2 |
| **Any other unanticipated toxicity** | |
| Grade 1-4 | Management as per CTCAE version 4.0 |

## 5.4 Usual Care

All participants in both study arms will receive usual care for treatment and prevention of delirium, including but not limited to behavioral interventions, psychiatric consultation, and psychotropic medications at the recommendation of psychiatric consultants and discretion of the bone marrow transplant team. This proposed standardized management of delirium is detailed in the attached protocol (Appendix A), which provides a framework to minimize variability in the treatment of delirium among study participants.

## 5.5 Prohibited Medications/Treatments

There are no medications/treatments that would prohibit subjects from inclusion and continued assessment in this study.

## 5.6 Duration of Therapy

Treatment will continue for seven days or until:

- Unacceptable adverse event(s)
- Inter-current illness that prevents further administration of treatment
- Subject decides to withdraw from the study, **OR**

Decisions to remove a subject from the trial or discontinuation of treatment before planned study completion will be undertaken in conjunction with consultation from the study PI or Co-PI.

## 5.7 Duration of Follow Up

For determination of study endpoints, subjects will be followed for six months after receiving HSCT or until death. Patients removed from study treatment for unacceptable AEs will be followed for resolution or stabilization of the adverse event(s). All patients (including those withdrawn for AEs) will be followed after removal from study treatment as stipulated in the protocol.

## 5.8 Study Withdrawal

Patients will be removed from protocol therapy and the PI notified when any of the criteria listed in section 5.6 apply. The reason for discontinuation of the protocol therapy will be documented on the eCRF.

If a patient decides to withdraw from the study (and not just from protocol therapy) an effort will be made to complete and report study assessments as thoroughly as possible. At the time of withdrawal, Drs. Nakamura or Rosenstein will attempt to establish as completely as possible the reason for the study withdrawal.

- The patient will be asked if they are willing to allow for the abstraction of relevant information from their medical record in order to meet the long-term follow up objectives outlined in the protocol.
- A complete final evaluation at the time of the patient's study withdrawal will be obtained with an explanation of why the patient is withdrawing from the study.
- If they are unwilling to come in for a final visit, then we will attempt to complete all assessments over the phone, through video conferencing, online, by email, or by mail that can be completed in this manner
- If the patient does not return for an end of study follow-up assessment, this will be documented in the eCRF.
- If the reason for removal of a patient from the study is an adverse event, the principal specific event will be recorded on the eCRF.

## 5.9 Study Questionnaires

### 5.9.1 Delirium Rating Scale (DRS)

The DRS is a is a 10-item, clinician-rated scale that rates the severity of delirium symptoms over a 24-hour period using all available information from the patient interview, mental status examination, medical history and tests, nursing observations, and family reports.[34] The maximum possible score is 32. A cut-off score of > 12 has been suggested to distinguish patients with delirium from patients with other neuropsychiatric disorders.[34,35] Each assessment will require up to 10 minutes of the subject's time.

### 5.9.2 Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT)

The FACT-BMT is a 47-item self-administered assessment which has been well validated in the literature and permits the measurement of HRQOL in bone marrow transplant patients.[36] It asks individuals to rate questions related to physical, social/family, emotional, and functional well-being on a 5-point Likert Scale (0, not at all to 4, very much). All participants who are enrolled in the trial will be evaluated pre-transplant and will have repeat assessment at one, three, and six month follow-up visits after transplant. If the subject exhibits difficulty in completing the assessment due to its length, the CRA will help the subject complete it by reading items and answer choices aloud. The FACT-BMT will take no greater than 15 minutes to complete.

### 5.9.3 Patient Reported Outcomes Measurement Information System – Depression (PROMIS-D)

The National Institute of Health's Patient-Reported Outcomes Measurement Information System (PROMIS) contains a depression bank.[37] We will use the PROMIS Depression 8a short form. Scores for all PROMIS measures are reported on the T-score metric in which the mean=50 and standard deviation (SD) = 10 are centered on the general population means. Higher scores represent greater degrees of mood symptoms. All participants who are enrolled in the trial will complete the self-administered assessment pre-transplant and will have repeat assessment at one, three, and six month follow-up visits after transplant. The PROMIS-D will take no greater than 5 minutes to complete.

### 5.9.4 Post Traumatic Stress Syndrome Scale 14 (PTSS-14)

The PTSS-14 is a 14-item self-administered assessment which has been well validated in the literature and permits the measurement of post-traumatic stress disorder (PTSD) symptoms.[38] It has been used in a variety of populations, including assessment following a period of delirium.[39] Questions are on a 7-point Likert-type Scale (1, never to 7, always) resulting in a total score between 14 and 98. Higher scores represent a more likely diagnosis of PTSD. All participants who are enrolled in the trial will be evaluated pre-transplant and will have repeat assessment at one, three, and six month follow-up visits after transplant. The PTSS-14 will take no greater than 10 minutes to complete.

### 5.9.5 Montreal Cognitive Assessment (MOCA)

The MOCA is a clinician administered tool which has been well validated in the literature, studied in a wide variety of patient populations, and permits assessment of cognitive impairment. It is measured on a 30-point scale with lower scores indicating greater impairment. Scores ≤ 25 are considered clinically significant. All participants who are enrolled in the trial will be evaluated at baseline and will have repeat assessment at one, three, and six month follow-up visits after transplant. The MOCA will take no greater than 10 minutes to complete.

### 5.9.6 Eastern Cooperative Oncology Group Performance Status (ECOG-PS)

The ECOG performance scale is one of the most widely used measures of functional status.[40] It has high reliability and validity and is frequently used to estimate prognosis and treatment eligibility in oncology clinical trials.[41] ECOG performance status is scored on a 6-point scale with higher scores representing greater physical restriction due to illness. The ECOG-PS will take no greater than 2 minutes to complete.

# 6.0 DRUG INFORMATION

## 6.1 Thiamine Description and Management

### 6.1.1 Mechanism of Action

Thiamine combines with adenosine triphosphate (ATP) to form thiamine pyrophosphate, also known as cocarboxylase, a coenzyme. Its role in carbohydrate metabolism is the decarboxylation of pyruvic acid in the blood and α-ketoacids to acetaldehyde and carbon dioxide.

### 6.1.2 Indications

Thiamine hydrochloride injection is indicated for the treatment of Wernicke's encephalopathy, Wernicke-Korsakoff syndrome, thiamine deficiency, beriberi (wet or dry), peripheral neuritis in pregnancy, and with dextrose-containing IV fluids.

### 6.1.3 How Supplied

The drug will be obtained from commercial supply through UNC Pharmacy and UNC Investigational Drug Service (IDS).

Full prescribing information for (Thiamine) is available at:
(http://editor.fresenius-kabi.us/PIs/Thiamine_Inj_45819E_May_08.pdf)

### 6.1.4 Dosage and Administration:

Subjects in the intervention group will receive Thiamine 200 mg IV tid.

**6.1.5 Storage and Stability**:
Thiamine should be stored at room temperature (between 68° to 77° F).

**6.1.6 Handling and Disposal**: Local requirements for disposal of hazardous drugs will be followed.

Please see UNC policy on hazardous drugs:
http://news.unchealthcare.org/empnews/att/2011/nov/admin0188/.

**6.1.7 Adverse Events Associated with Commercial Drug**

In a study of 989 patients given a rapid IV push of 100 mg IV thiamine, the only identified side effects were immediate, transient burning (1.02%) and generalized pruritis (0.093%).[27] Anaphylaxis has been reported at a rate of one reaction per every 5 million ampules used.[28] The following have also been reported with unknown frequency: a feeling of warmth, weakness, sweating, nausea, restlessness, tightness of the throat, angioneurotic edema, cyanosis, pulmonary edema, and hemorrhage into the gastrointestinal tract. Parenteral doses of 100 to 500 mg singly have been administered without adverse effect.[29] A comprehensive list of adverse effects can be found at the following web address: http://editor.fresenius-kabi.us/PIs/Thiamine_Inj_45819E_May_08.pdf

# 7.0 EVALUATIONS AND ASSESSMENTS

## 7.1 Time and Events Table

| | Baseline (Pre-Transplant) | Post-Transplant Day 1 | Post-Transplant Days 2 – 30 | F1[c] | F2 | F3 |
|---|---|---|---|---|---|---|
| Informed Consent | • | | | | | |
| Group Assignment | • | | | | | |
| Demographic Data Form | • | | | | | |
| Cancer History Form | • | | | | | |
| Delirium Risk Factor Form | • | • | • | | | |
| Concurrent CNS Active Medication Tracking Form | • | • | • | | | |
| Baseline Labs[a] | | • | | | | |
| Thiamine Levels[b] | | • | • | | | |
| FACT-BMT[c] | • | | | • | • | • |
| PROMIS-D[c] | • | | | • | • | • |
| PTSS-14[c] | • | | | • | • | • |
| MOCA[c] | • | | | • | • | • |
| ECOG-PS[c] | • | | | • | • | • |
| DRS[d] | • | • | • | | | |
| Adverse Events Form | | • | • | | | |

a. Complete Blood Count (CBC), Comprehensive Metabolic Panel (CMP), Magnesium (Mg), Phosphorus (Phos)
b. Thiamine levels will be drawn on post-transplant day 1, 8 days post-transplant, 15 days post-transplant, 22 days post-transplant, and 29 days post-transplant.
c. FACT-BMT, PROMIS-D, PTSS-14, MOCA, and ECOG-PS will be performed at baseline (pre-transplant) and at one (F1), three (F2), and six months (F3) after transplant.
d. DRS will be performed at baseline, on post-transplant day 1, and three times weekly thereafter. If a participant is identified as having delirium, assessments will increase to daily until delirium resolves at which point frequency will resume at three times weekly. For participants who develop delirium during the inpatient phase, DRS will be performed at one (F1), three (F2), and six months (F3) after transplant.

## 7.2 Pre-Study (Baseline) Assessments

Patients scheduled for admission to the UNC Bone Marrow Transplant unit will be considered for enrollment in this trial. Prior to transplant, the clinical research assistant (CRA) will review the trial with the subject, obtain informed consent, and the subject will complete self-report assessments for depression (PROMIS-D), post-traumatic stress symptoms (PTSS-14), and HRQOL (FACT-BMT), as well as clinician-rated assessments of cognition (MOCA), functional status (ECOG-PS), and for delirium (DRS). See Appendices A – F. The CRA or investigators will also conduct a review of electronic medical records to obtain baseline information regarding delirium risk factors, the subject's cancer and cancer treatment, and demographic information.

## 7.3 Randomization

If the patient meets all inclusion/exclusion criteria, provides informed consent, and is not delirious (DRS≤12), the subjects will then be randomized in a 1:1 ratio to the intervention or control arms in a double-blind fashion such that the investigators, biostatistician, CRA(s), nursing staff, and subjects will not know which agent is being administered. The statistician of record will design a block randomization scheme, stratified by age (<65 or ≥65) and baseline cognitive function (MOCA >25 or ≤25), both well-known risk factors for delirium. This information will be provided to UNC Investigational Drug Services, who will manage the actual assignment of subjects to each arm using the randomization list designed by the statistician.

## 7.4 Post-Transplant Days 1 – 30 Assessments

Within two days of transplant, the subject will have a CBC, CMP, Mg level, Phos level, and Thiamine level drawn. The CRA(s) or investigators will perform the delirium assessment (DRS), and a brief history will be obtained to assess for any toxicity from therapy.

Over the course of 30 days following transplant (or discharge, whichever comes first), the subject will continue to have weekly thiamine levels drawn (at days 8, 15, 22, and 29 +/- one day). The CRA(s) or investigators will continue to assess for delirium, using the DRS, three times weekly. If a subject is determined to

have delirium, frequency of delirium assessments will increase to daily, Monday through Friday, as scheduling permits, until delirium resolves. The DRS assessments will not be performed if a patient becomes unevaluable due to an acute medical concern (e.g. intubation, sedation, etc.). The CRA(s) or investigators will continue to assess for any toxicity from therapy.

### 7.5 Long-term Follow-Up Assessments

At one, three, and six months post-transplant the CRA(s) or investigators will meet with subjects to complete self-report assessments for depression (PROMIS-D), post-traumatic stress symptoms (PTSS-14), and HRQOL (FACT-BMT), as well as clinician-rated assessments of cognition (MOCA) and functional status (ECOG-PS). At the time of each follow-up, delirium assessments (DRS) will also be performed in participants who became delirious during the inpatient phase. Subjects will receive reminders regarding these long-term assessments via subjects' preferred method of contact. Long-term assessments will occur at one month (+/- two weeks), three months (+/- four weeks), and six months (+/- two months). The specified window at each of these follow-up time points will allow for assessments to coincide with BMT clinic visits. If a face to face assessment is not feasible, attempts will be made to perform assessments over the phone, through video conferencing, online, by email, or by mail. When assessments cannot be completed, this will be noted in the eCRF.

### 7.6 Concurrent CNS Active Medications

All concurrent CNS active medications, including antidepressants, anxiolytics, antipsychotics, antiepileptics, and antihistamines will be documented at Baseline/Screening and throughout the study as summarized in the Time and Events Table in Section 7.1.

### 7.7 Demographics

Demographic information (date of birth, gender, race) will be recorded by the CRA from review of medical records at baseline.

### 7.8 Delirium Risk Factors

Relevant risk factors for delirium, including previous history of delirium, alcohol and substance use, and neurological conditions (stroke, traumatic brain injury, seizures, abnormal findings on imaging) will be abstracted from medical records at baseline.

### 7.9 Handling of Biospecimens Collected for Correlative Research

Biospecimens for this study will be collected by a registered nurse and stored in the McLendon laboratories. Blood samples will then be sent Mayo Medical

Laboratories for assay of thiamine levels. Each sample will be assigned a unique code number and no identifiable personal health information (PHI) will be on the specimen label. Researchers with IRB-approval for access to PHI for each subject in this study will be able to link specimens to relevant medical information.

**Storage Time:**

- The biospecimen will be used first and foremost for research purposes outlined within the confines of this protocol. Samples will be discarded/destroyed after relevant data are collected for this study, unless consent was obtained from the patient to use his/her blood for other research purposes (e.g., consent form was signed by the patient). In this circumstance, there is no time limit on how long biospecimens may be stored.

**Compliance Statement**

Biospecimen collection for this study will be conducted in full accordance with all applicable University of North Carolina (UNC) Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, and the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. Any episode of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent (unless a waiver is granted), and will report unexpected problems in accordance with The UNC IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

## 7.10 Assessment of Safety

Any patient who receives at least one dose of study therapy on this protocol will be evaluable for toxicity. Each patient will be assessed periodically for the development of any toxicity according to the Time and Events table. Toxicity will be assessed according to the NCI CTCAEv4.0.3.

## 7.11 Assessment of Efficacy

In order to be considered evaluable for efficacy, patients must:

- receive all 7 days of the treatment; a patient must receive at least 17/21 (80%) thiamine doses
- have delirium assessed at least weekly until one of the following is met:
    1. The participant is found to be delirious (DRS>12)
    2. The participant is at least 30 days post-transplant
    3. The participant is discharged

If a patient is deemed not evaluable, they will be replaced by a new patient. However, if a patient develops delirium during the intervention, they will still

receive the full 7 day course, not be replaced, and included in the efficacy analysis.

# 8.0 ADVERSE EVENTS

## 8.1 Definitions

### 8.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence (e.g., an abnormal laboratory finding, symptom, or disease temporally associated with the use of a drug) in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Development or worsening of delirium should not be recorded as an AE, unless it is attributable by the investigator to the study therapy.

### 8.1.2 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the drug is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Causality assessment to a study drug is a medical judgment made in consideration of the following factors: temporal relationship of the AE to study drug exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug exposures, normal clinical course of the disease under investigation, and any other underlying or concurrent medical conditions. Other factors to consider in considering drug as the cause of the AE:

- Single occurrence of an uncommon event known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event not commonly associated with drug exposure, but otherwise uncommon in the population (e.g., tendon rupture); often more than once occurrence from one or multiple studies would be needed before the sponsor could determine that there is *reasonable possibility* that the drug caused the event.

- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the drug treatment group than in a concurrent or historical control group

### 8.1.3 Unexpected AE or SAR

An AE or SAR is considered unexpected if the specificity or severity of it is not consistent with the applicable product information (e.g., package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

### 8.1.4 Serious AE or SAR

An AE or SAR is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization (>24 hours) or prolongation of existing hospitalization;*
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

Pregnancy that occurs during the study must also be reported as an SAE.

## 8.2 Documentation of non-serious AEs or SARs

For non-serious AEs or SARs, documentation must begin from day 1 of study treatment and continue through the 30 day follow-up period after treatment is discontinued.

Collected information should be recorded in the Case Report Forms (CRF) for that patient. Please include a description of the event, its severity or toxicity grade, onset and resolved dates (if applicable), and the relationship to the study drug. Documentation should occur at least monthly.

## 8.3 SAEs or Serious SARs

### 8.3.1 Timing

After informed consent but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g. SAEs related to invasive procedures such as biopsies, medication washout).

For any other experience or condition that meets the definition of an SAE or a serious SAR, recording of the event must begin from day 1 of study treatment and continue through the 30 day follow-up period after treatment is discontinued.

### 8.3.2 Documentation and Notification

SAEs or Serious SARs must be recorded in the SAE console within Oncore™ for that patient within 24 hours of learning of its occurrence. Additionally, the NCCN Project Manager must also be notified via email of all SAEs within 24 hours of learning of its occurrence.

## 8.4 Adverse Event Reporting

### 8.4.1 IRB Reporting Requirements:

UNC:

- The UNC-IRB will be notified of all SAEs that qualify as an Unanticipated Problem as per the UNC IRB Policies using the IRB's web-based reporting system (see section 10.5.3) within 7 days of the Investigator becoming aware of the problem.

### 8.4.2 Funding Source (e.g. Manufacturer) Reporting Requirements:

N/A

## 8.5 Data and Safety Monitoring Plan

This is a Phase II, single site study of 60 individuals to gather preliminary data on the efficacy and safety of high dose IV thiamine for delirium prevention in patients undergoing HSCT. We will follow our standard protocol for monitoring of clinical trials. Subjects are screened to ensure that there are no contraindications to their participation.

The study Co-PIs, Drs. Nakamura and Rosenstein, will be responsible for continuous monitoring of patient safety during the trial. For non-serious Adverse Events (AEs), documentation will begin from the first day of study treatment and continue through the 30 day follow-up period after treatment is discontinued. Collected information will be recorded in Case Report Forms (CRF) for that patient. A description of the event, its

severity or toxicity grade, onset and resolved dates (if applicable), and the relationship to the study drug will be included. For any experience or condition that meets the definition of a serious adverse event (SAE), recording of the event will begin after signing of the informed consent and continue through the 30 day follow-up period after treatment is discontinued. These events will be recorded in the CRF for that patient within 24 hours of learning of its occurrence. If the event is both serious AND unexpected, it will also be recorded on the MedWatch Form 3500A, as per 21 CFR 312.32, and forwarded to the FDA in accordance with 21 CFR 314.80 (for marketed drugs). The UNC IRB will be notified of all SAEs that qualify as an Unanticipated Problem (serious, unexpected, and related) as per the UNC IRB policies. In accordance with these policies, an aggregated list of all SAEs will be submitted to the UNC IRB annually at the time of study renewal.

Periodic review, at an interval of every six months to annually, by the Lineberger Comprehensive Cancer Center Data Safety Committee (LCC DSMC), Protocol Review Committee (PRC), and Office of Human Research Ethics (OHRE) Biomedical IRB will provide oversight of the Co- PIs' continuous monitoring. For each DSMC review, summary information regarding toxicity and accrual patterns will be prepared and submitted by the Co-PIs. Specific information submitted for review includes: (1) The number of patients enrolled, consented, consented but not treated, currently being treated, completed treatment, the number of patients who did not complete treatment and the reasons for coming off study; (2) Grade 3 or greater reported Adverse Events to date; (3) Serious Adverse Events and Unanticipated Problems since last report, with assurance of reporting to internal and external regulating bodies; (4) Exceptions in eligibility or treatment and significant protocol deviations/violations; (5) Significant literature reporting developments that may affect the safety of participants or the ethics of the study; (6) Summaries of team meetings that have occurred since the last report; (7) Results of interim analyses required by the protocol. We will also be submitting a preliminary report of response and other endpoints listed in the primary and secondary objectives of the protocol for DSMC review.

Though no formal *a priori* stopping rules are proposed for the study, in the event of a serious or unexpected adverse event or frequent occurrence of less serious unexpected or expected adverse events we will consult with the OHRE and DSMC as to whether the trial should continue.

# 9.0 STATISTICAL CONSIDERATIONS

## 9.1 Study Design/Study Endpoints

This is a randomized double-blind controlled trial in participants undergoing allogeneic hematopoietic stem cell transplantation (HSCT) to evaluate if high dose intravenous (IV) thiamine can prevent delirium and minimize the deleterious impact of delirium on health-related quality of life (HRQOL), functional status, and other neuropsychiatric outcomes. We will recruit 60 evaluable patients scheduled for allogeneic HSCT at UNC, randomize them to treatment with high

dose IV thiamine (n = 30) versus placebo (n = 30), and systematically evaluate all participants for delirium and related comorbidities.

Analysis Populations: The Safety Population will be defined as all subjects who were enrolled and received at least one dose of study medication. Efficacy Evaluable Population will be defined as all subjects who received at least 80% (17/21) of total possible intervention doses and participated in at least one delirium assessment weekly.

The primary efficacy endpoint is delirium incidence defined as DRS >12. Secondary endpoints include delirium duration and severity, along with FACT-BMT, PROMIS-D, PTSS-14, ECOG-PS, and MOCA.

## 9.2 Sample Size, Accrual and Duration of Accrual

For the primary objective of comparing delirium incidence between groups, a two group chi-squared test with a 0.050 one-sided significance level will have 80% power to detect the difference between a usual care proportion of 0.445 and an intervention proportion of 0.155 (odds ratio of 0.229) when the evaluable sample size in each group is 30. The anticipated rate of delirium in the control group is based on 43 – 73% incidence of delirium during hospitalization for HSCT reported in the literature. As this is the first study to evaluate the efficacy of thiamine as a prevention strategy for delirium, no data is available to generate an estimate of delirium incidence in the intervention group. However, the odds ratio (OR) hypothesized for this study is in line with other successful delirium prevention trials.[42,43] Even if the delirium incidence in the IV thiamine group is not this low, the results of this study will provide effect sizes and 95% confidence intervals to power a future larger study.

Our sample will include 60 adult participants. UNC tumor registry records demonstrate that between 2015 and 2016 133 patients were admitted for allogeneic stem cell transplant. We estimate that we will enroll at least 50% of eligible patients, based on recruitment rates described in previous delirium intervention studies,[44] allowing us to recruit our target of 60 evaluable participants in approximately two years and complete our study in the proposed three year grant period.

## 9.3 Data Analysis Plans

<u>To compare delirium incidence, severity, and duration between recipients of high dose IV thiamine and placebo during hospitalization for HSCT</u>. The primary outcome measure is delirium incidence, defined as: DRS > 12. Secondary outcomes are differences in delirium duration (in days) and delirium severity, in which higher DRS scores suggest more severe delirium. A two group chi-squared test will be used to compare rates of delirium in the intervention and control group. Maximum severity score will be analyzed using two group t-tests, and time to delirium will be compared between groups using the Kaplan-Meier

method. For those with delirium, two group t-tests will compare the duration of delirium between intervention groups; Kaplan-Meier methods may also be considered for time to delirium resolution.

To determine if thiamine status is predictive of future delirium onset. We will examine the relationship between thiamine levels at the end of the seven day administration of thiamine and the development of delirium at any point during the thirty days post-transplant or the post-transplant hospitalization, whichever comes first. Patients who develop delirium prior to the end of the thiamine treatment will not be included in this analysis. We will examine the sensitivity and specificity of this relationship with ROC curves, and attempt to find a cutoff for thiamine levels that is associated with the development of delirium.

To investigate the effects of high dose IV thiamine on long-term health-related quality of life (HRQOL), functional status, depression, post-traumatic stress symptoms, and cognitive functioning in patients hospitalized for HSCT. Scores on FACT-BMT, PROMIS-D, PTSS-14, ECOG-PS and MOCA will be compared between intervention and control groups. We will summarize scores on the FACT-BMT, PROMIS-D, PTSS-14, ECOG-PS, and MOCA between the intervention and control groups at one, three, and six months post-transplant. Longitudinal modeling will be performed to examine differences/changes over time.

Safety Analyses: We will tabulate AEs and SAEs, by treatment and placebo, within strata. We will include all AEs which occurred at a rate of more than 5% in any treatment.

# 10.0 STUDY MANAGEMENT

## 10.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that

the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

## 10.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Protocol Office (CPO) at the University of North Carolina.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any sub-investigators who will be involved in the study.
- The Investigator's signature documenting understanding of the protocol and providing commitment that this trial will be conducted according to all stipulations of the protocol is sufficient to ensure compliance
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

## 10.3 Registration Procedures

All patients must be registered with the CPO at the University of North Carolina before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the UNC Study Coordinator. To register a patient call the CPO at 919-966-4432 Monday-Friday 9:00 am – 5:00 pm EST or email the UNC Project Manager.

## 10.4 Data Management and Monitoring/Auditing

The CPO of the UNC LCCC will serve as the coordinating center for this trial. Data will be collected through a web based clinical research platform, OnCore®. All data will be collected and entered into OnCore® by research coordinators from UNC LCCC.

The sponsor will provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection. As an investigator initiated study, this trial will also be audited by the LCCC compliance committee every six or twelve months.

## 10.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

### 10.5.1 Emergency Modifications

UNC investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC IRB approval.

For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

### 10.5.2 Single Patient/Subject Exceptions

Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the UNC Principal Investigator and the UNC IRB.

### 10.5.3 Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs please follow the guidelines below:

**Protocol Deviations:** UNC or Affiliate personnel will record the deviation in OnCore®, and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

**Protocol Violations:** Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

**Unanticipated Problems:** Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must be reported by the study personnel using the IRB's web-based reporting system.

## 10.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

## 10.7 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor correspondence to Investigators, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

## 10.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study

staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator will be responsible for assuring that all the required data will be collected and entered into the eCRFs. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all eCRFs will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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# 12.0 APPENDICES

## Appendix A: Suggested Management of Delirium

1. Obtain further laboratory work-up[45,46]

*In all patients with delirium the following should be considered:*

- Blood chemistries: electrolytes, glucose, calcium, albumin, blood urea nitrogen (BUN), creatinine, AST, ALT, bilirubin, alkaline phosphatase, magnesium, phosphorus
- Complete blood count (CBC)
- Electrocardiogram
- Chest X-ray
- Measurement of arterial blood gases or oxygen saturation
- Urinalysis

*In patients with delirium the following should be considered if felt to be clinically indicated:*

- Urine culture and sensitivity
- Urine drug screen
- Blood cultures
- Measurement of serum levels of medications (e.g., tacrolimus, cyclosporine, etc.)
- Lumbar puncture
- Brain computerized tomography (CT) or magnetic resonance imaging (MRI)
- Electroencephalogram (EEG)
- Folate, B12

2. Treat any reversible abnormalities identified in work-up

3. Initiate environmental and supportive interventions
   - Staff to open blinds every morning.
   - Glasses, hearing aide, and patient's own shoes to bedside. Make available to patients when possible and encourage use.
   - Encourage po fluids when appropriate, keep fluids within reach.
   - Out of bed to chair with meals.
   - Staff to assess orientation to person, time and place every morning and as needed throughout the day.
   - Recommend extended visitation hours with familiar family/friends as feasible.
   - Staff to minimize disturbances at night. Turn off television when patient asleep or when not in use.

4. Consult Psychiatry for a.) behavioral disturbance and/or b.) Delirium Rating Score > 12

*Note: With the exception of urgent psychiatric consults needed overnight, on weekends, or on holidays, consultants will be limited to study investigators Drs. Nakamura and Rosenstein.*

# Appendix B: DELIRIUM RATING SCALE (DRS)

## 1. Temporal onset of symptoms

| | | |
|---|---|---|
| | 0 | No significant change from longstanding behavior, essentially a chronic or chronic-recurrent disorder |
| | 1 | Gradual onset of symptoms, occurring within a 6-month period |
| | 2 | Acute change in behavior or personality occurring over a month |
| | 3 | Abrupt change in behavior, usually occurring over a 1- to 3-day period |

## 2. Perceptual disturbances

| | | |
|---|---|---|
| | 0 | None evident by history or observation |
| | 1 | Feelings of depersonalization or derealization |
| | 2 | Visual illusions or misperceptions including macropsia, micropsia; e.g., may urinate in wastebasket or mistake bedclothes for something else |
| | 3 | Evidence that the patient is markedly confused about external reality; e.g., not discriminating between dreams and reality |

## 3. Hallucination type

| | | |
|---|---|---|
| | 0 | Hallucinations not present |
| | 1 | Auditory hallucinations only |
| | 2 | Visual hallucinations present by patient's history or inferred by observation, with or without auditory hallucinations |
| | 3 | Tactile, olfactory, or gustatory hallucinations present with or without visual or auditory hallucinations |

## 4. Delusions

| | | |
|---|---|---|
| | 0 | Not present |
| | 1 | Delusions are systematized, i.e., well-organized and persistent |
| | 2 | Delusions are new and not part of a preexisting primary psychiatric disorder |
| | 3 | Delusions are not well circumscribed; are transient, poorly organized, and mostly in response to misperceived environmental cues; e.g., are paranoid and involve persons who are in reality caregivers, loved ones, hospital staff, etc. |

## 5. Psychomotor behavior

| | | |
|---|---|---|
| | 0 | No significant retardation or agitation |

| | | |
|---|---|---|
| | 1 | Mild restlessness, tremulousness, or anxiety evident by observation and a change from patient's usual behavior |
| | 2 | Moderate agitation with pacing, removing i.v.'s, etc. |
| | 3 | Severe agitation, needs to be restrained, may be combative; or has significant withdrawal from the environment, but not due to major depression or schizophrenic catatonia |

## 6. Cognitive status during formal testing

| | | |
|---|---|---|
| | 0 | No cognitive deficits, or deficits which can be alternatively explained by lack of education or prior mental retardation |
| | 1 | Very mild cognitive deficits which might be attributed to inattention due to acute pain, fatigue, depression, or anxiety associated with having a medical illness |
| | 2 | Cognitive deficit largely in one major area tested, e.g., memory, but otherwise intact |
| | 3 | Significant cognitive deficits which are diffuse, i.e., affecting many different areas tested; must include periods of disorientation to time or place at least once each 24-hr period; registration and/or recall are abnormal; concentration is reduced |
| | 4 | Severe cognitive deficits, including motor or verbal perseverations, confabulations, disorientation to person, remote and recent memory deficits, and inability to cooperate with formal mental status testing |

## 7. Physical disorder

| | | |
|---|---|---|
| | 0 | None present or active |
| | 1 | Presence of any physical disorder which might affect mental state |
| | 2 | Specific drug, infection, metabolic, central nervous system lesion, or other medical problem which can be temporally implicated in causing the altered behavior or mental status |

## 8. Sleep-wake cycle disturbance

| | | |
|---|---|---|
| | 0 | Not present; awake and alert during the day, and sleeps without significant disruption at night |
| | 1 | Occasional drowsiness during day and mild sleep continuity disturbance at night; may have nightmares but can readily distinguish from reality |

| | | |
|---|---|---|
| | 2 | Frequent napping and unable to sleep at night, constituting a significant disruption of or a reversal of the usual sleep-wake cycle |
| | 3 | Drowsiness prominent, difficulty staying alert during interview, loss of self-control over alertness and somnolence |
| | 4 | Drifts into stuporous or comatose periods |

## 9. Lability of mood

| | | |
|---|---|---|
| | 0 | Not present; mood stable |
| | 1 | Affect/mood somewhat altered and changes over the course of hours; patient states that mood changes are not under self-control |
| | 2 | Significant mood changes which are inappropriate to situation, including fear, anger, or tearfulness; rapid shifts of emotion, even over several minutes |
| | 3 | Severe disinhibition of emotions, including temper outbursts, uncontrolled inappropriate laughter, or crying |

## 10. Variability of symptoms

| | | |
|---|---|---|
| | 0 | Symptoms stable and mostly present during daytime |
| | 2 | Symptoms worsen at night |
| | 4 | Fluctuating intensity of symptoms, such that they wax and wane during a 24-hr period |

## Appendix C: Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT)

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

| | **PHYSICAL WELL-BEING** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| 1 | I have a lack of energy | 0 | 1 | 2 | 3 | 4 |
| 2 | I have nausea | 0 | 1 | 2 | 3 | 4 |
| 3 | Because of my physical condition, I have trouble meeting the needs of my family | 0 | 1 | 2 | 3 | 4 |
| 4 | I have pain | 0 | 1 | 2 | 3 | 4 |
| 5 | I am bothered by side effects of treatment | 0 | 1 | 2 | 3 | 4 |
| 6 | I feel sick | 0 | 1 | 2 | 3 | 4 |
| 7 | I am forced to spend time in bed | 0 | 1 | 2 | 3 | 4 |
| 8 | Looking at the above 7 questions, how much would you say your Physical Well-Being affects your quality of life? | 0 1 2 3 4 5 6 7 8 9 10<br>Not at all Very much so | | | | |

| | **SOCIAL/FAMILY WELL-BEING** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| 9 | I feel distant from my friends | 0 | 1 | 2 | 3 | 4 |
| 10 | I get emotional support from my family | 0 | 1 | 2 | 3 | 4 |
| 11 | I get support from my friends and neighbors | 0 | 1 | 2 | 3 | 4 |
| 12 | My family has accepted my illness | 0 | 1 | 2 | 3 | 4 |
| 13 | Family communication about my illness is poor | 0 | 1 | 2 | 3 | 4 |
| 14 | I feel close to my partner (or the person who is my main support) | 0 | 1 | 2 | 3 | 4 |
| 15 | Have you been sexually active during the past year?<br><br>No ___ Yes ___ If yes: I am satisfied with my sex life | 0 | 1 | 2 | 3 | 4 |
| 16 | Looking at the above 7 questions, how much would you say your Social/Family Well-Being affects your quality of life? | 0 1 2 3 4 5 6 7 8 9 10<br><br>Not at all | | | | Very much so |

| | **RELATIONSHIP WITH DOCTOR** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| 17 | I have confidence in my doctor(s) | 0 | 1 | 2 | 3 | 4 |
| 18 | My doctor is available to answer my questions | 0 | 1 | 2 | 3 | 4 |
| 19 | Looking at the above 2 questions, how much would you say your Relationship with the Doctor affects your quality of life? | 0 1 2 3 4 5 6 7 8 9 10<br><br>Not at all | | | | Very much so |

| | **EMOTIONAL WELL-BEING** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| 20 | I feel sad | 0 | 1 | 2 | 3 | 4 |
| 21 | I am proud of how I am coping with my illness | 0 | 1 | 2 | 3 | 4 |
| 22 | I am losing hope in the fight against my illness | 0 | 1 | 2 | 3 | 4 |
| 23 | I feel nervous | 0 | 1 | 2 | 3 | 4 |
| 24 | I worry about dying | 0 | 1 | 2 | 3 | 4 |
| 25 | I worry that my condition will get worse | 0 | 1 | 2 | 3 | 4 |
| 26 | Looking at the above 6 questions, how much would you say your Emotional Well-Being affects your quality of life? | 0 1 2 3 4 5 6 7 8 9 10<br>Not at all Very much so | | | | |

| | **FUNCTIONAL WELL-BEING** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| 27 | I am able to work (include work at home) | 0 | 1 | 2 | 3 | 4 |
| 28 | My work (include work at home) is fulfilling | 0 | 1 | 2 | 3 | 4 |
| 29 | I am able to enjoy life | 0 | 1 | 2 | 3 | 4 |
| 30 | I have accepted my illness | 0 | 1 | 2 | 3 | 4 |
| 31 | I am sleeping well | 0 | 1 | 2 | 3 | 4 |
| 32 | I am enjoying the things I usually do for fun | 0 | 1 | 2 | 3 | 4 |
| 33 | I am content with the quality of my life right now | 0 | 1 | 2 | 3 | 4 |
| 34 | Looking at the above 7 questions, how much would you say your Functional Well-Being affects your quality of life? | 0 1 2 3 4 5 6 7 8 9 10<br>Not at all Very much so | | | | |

| | **ADDITIONAL CONCERNS** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| 35 | I am concerned about keeping my job (include work at home) | 0 | 1 | 2 | 3 | 4 |
| 36 | I feel distant from other people | 0 | 1 | 2 | 3 | 4 |
| 37 | I worry that the transplant will not work | 0 | 1 | 2 | 3 | 4 |
| 38 | The effects of treatment are worse than I had imagined | 0 | 1 | 2 | 3 | 4 |
| 39 | I have a good appetite | 0 | 1 | 2 | 3 | 4 |
| 40 | I like the appearance of my body | 0 | 1 | 2 | 3 | 4 |
| 41 | I am able to get around by myself | 0 | 1 | 2 | 3 | 4 |
| 42 | I get tired easily | 0 | 1 | 2 | 3 | 4 |
| 43 | I am interested in having sex … | 0 | 1 | 2 | 3 | 4 |
| 44 | I have concerns about my ability to have children | 0 | 1 | 2 | 3 | 4 |
| 45 | I have confidence in my nurse(s) | 0 | 1 | 2 | 3 | 4 |
| 46 | I regret having the bone marrow transplant | 0 | 1 | 2 | 3 | 4 |
| 47 | Looking at the above 12 questions, how much would you say these Additional Concerns affect your quality of life? | 0 1 2 3 4 5 6 7 8 9 10<br>Not at all Very much so | | | | |

# Appendix D: Patient Reported Outcomes Measurement Information System – Depression (PROMIS-D)

**Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.** Mark only one box per row.

| | | Never | Rarely | Sometimes | Often | Always |
|---|---|---|---|---|---|---|
| 1 | I felt worthless | 1 | 2 | 3 | 4 | 5 |
| 2 | I felt helpless | 1 | 2 | 3 | 4 | 5 |
| 3 | I felt depressed | 1 | 2 | 3 | 4 | 5 |
| 4 | I felt hopeless | 1 | 2 | 3 | 4 | 5 |
| 5 | I felt like a failure | 1 | 2 | 3 | 4 | 5 |
| 6 | I felt unhappy | 1 | 2 | 3 | 4 | 5 |
| 7 | I felt that I had nothing to look forward to | 1 | 2 | 3 | 4 | 5 |
| 8 | I felt that nothing could cheer me up | 1 | 2 | 3 | 4 | 5 |

# Appendix E: Post-Traumatic Stress Symptom Scale (PTSS-14)

**Please circle or mark one number per line to indicate your response as it applies to the <u>past few days</u>.** Mark only one box per row.

**Presently I suffer from:**

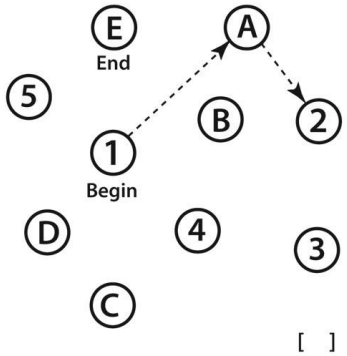
| | | Never | | | | | | Always |
|---|---|---|---|---|---|---|---|---|
| 1 | Sleep Problems | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 2 | Nightmares | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 3 | Depression, I feel dejected/downtrodden | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 4 | Jumpiness, I am easily frightened by sudden sounds or sudden movements | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 5 | The need to withdraw from others | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 6 | Irritability, that is, I am easily agitated/annoyed and angry | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 7 | Frequent mood swings | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 8 | A bad consciences, blame myself, have feelings of guilt | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 9 | Fear of places and situations, which remind me of the Bone Marrow Transplant Unit | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 10 | Muscular tension | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 11 | Upsetting, unwanted thoughts or images of my time on the Bone Marrow Transplant Unit | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 12 | Feeling numb (e.g. cannot cry, unable to have loving feelings) | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 13 | Avoid places, people or situations that remind me of the Bone Marrow Transplant Unit | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 14 | Feeling as if my plans or dreams for the future will not come true | 1 | 2 | 3 | 4 | 5 | 6 | 7 |

# Appendix F: Montreal Cognitive Assessment (MOCA)

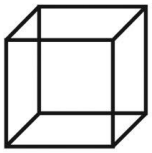
**MONTREAL COGNITIVE ASSESSMENT (MOCA)**
Version 7.1 Original Version

**NAME :**
**Education :** **Date of birth :**
**Sex :** **DATE :**

**VISUOSPATIAL / EXECUTIVE** — POINTS




Copy cube

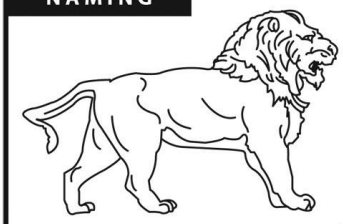


[ ] [ ]

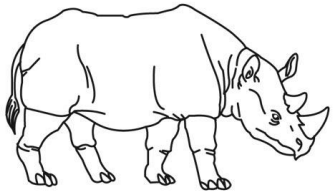
Draw CLOCK (Ten past eleven) ( 3 points )

[ ] Contour [ ] Numbers [ ] Hands __/5

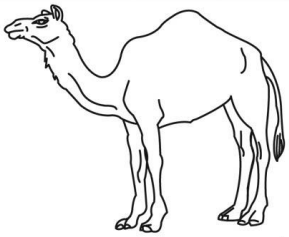
**NAMING**



[ ]



[ ]



[ ] __/3

**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 [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** __/3

**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. [ ] __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) __/1

**ABSTRACTION** Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler __/2

**DELAYED RECALL**

| | Has to recall words **WITH NO CUE** | FACE [ ] | VELVET [ ] | CHURCH [ ] | DAISY [ ] | RED [ ] | Points for UNCUED recall only |
|---|---|---|---|---|---|---|---|
| **Optional** | Category cue | | | | | | |
| | Multiple choice cue | | | | | | |

__/5

**ORIENTATION** [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

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TOTAL __/30
Add 1 point if ≤ 12 yr edu

Administered by: _____

# Appendix G: Eastern Cooperative Oncology Group Performance Status (ECOG-PS)

| ECOG | Description |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction. |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work. |
| 2 | Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 3 | Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours. |
| 4 | Completely disabled. Cannot carry on selfcare. Totally confined to bed or chair |

a