Protocol Title: A Proof-of-Concept Trial on the Effect of Ketamine on Fatigue Abbreviated Title: Ketamine on Fatigue

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

PRECIS

Purpose: The purpose of the study is to investigate the anti-fatigue effects of ketamine in individuals with chronic illness.

Background: Although the underlying mechanisms of fatigue have been studied in several disease conditions (Bower et al., 2002; Brola et al., 2007), the etiology, mechanisms, and risk factors remain elusive and this symptom remains poorly managed. Fatigue is conceptualized as a multidimensional symptom which incorporates temporal, sensory, cognitive/mental, affective/emotional, behavioral, and physiological dimensions (Voss, et al., 2006). It is described as a common, chronic, and disabling symptom in individuals with Sjögren's syndrome (Ng et al., 2012) and those with systemic lupus erythematosus (Fonsecaet al., 2014). We recently observed that upregulation of glutamate receptors (e.g., GRM5) can predict individuals who will develop chronic fatigue one year after completing cancer therapy, suggesting that fatigue may share common glutamatergic markers with depression .Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist and has been reported to have rapid anti-depressant effects (Berman et al., 2000; Prommer, 2012; Aan Het Rot etal., 2012), and we recently found that it also has rapid anti-fatigue effects (Saligan et al., 2016). Evidence suggest that severe fatigue in diverse medical conditions is driven by similar biological mechanisms, hence identifying a potential anti-fatigue agent in one medical condition may be a valuable anti-fatigue therapy for other fatiguing conditions.

Population for Study: This proof-of-concept study will enroll 59 individuals (target n of completers

= 50) with chronic fatigue.

Key Inclusion/Exclusion Criteria: Participants must have a fatigue visual analog scale (VAS) score of ≥ 50 mm (on a 0-100 mm horizontal scale). The ≥ 50 mm fatigue VAS score is considered clinically important fatigue cutoff score for patients with chronic illness (Klokkerud et al., 2017; Minnock et al., 2009), and also captures the effectivity outcome of a previous pharmacologic intervention for fatigue (Kamath et al., 2012). The participants must not have any progressive or unstable conditions or be taking medications that cause fatigue.

Methodology: This is a phase II, randomized, double-blind (study team and participants), active comparator- controlled, cross-over trial. After determining eligibility during the screening visit, the participant will be randomized to determine the sequence of study drug/active comparator to take during each phase.

Main Study Events / Estimates of Duration and Time Commitments: The study has two periods, and each period is approximately two weeks long (total of four weeks). The study (both periods, excluding the screening visit) will require eight NIH outpatient visits and three phone calls.

Primary and Representative Secondary Outcomes: The primary outcome measure of the study is the change in self-reported fatigue VAS score before and three days after receiving ketamine or active comparator (midazolam). A 20% decrease in fatigue VAS score three days after ketamine treatment will be considered the primary indicator of efficacy in this study. The secondary outcomes of this study include: symptoms, physical activity count, skeletal muscle strength, motivation score, cognitive function test scores, changes in gene expression or protein levels of pro- inflammatory markers (e.g., lymphotoxin, IFNγ, TNFα) typically seen in fatigue, and

neurometabolite (e.g., BDNF) levels and mitochondrial markers (e.g., glucose transporter 4) before and after a dose of ketamine or active comparator.

General Analytic Plans: A linear mixed model with restricted maximum likelihood estimation will be used to examine changes in fatigue symptoms over the course of the trial where all participants with at least a pre-dose and one post-dose measure will be included. Within-subjects factors will include time with pre-dose and all other points. The interaction between time and ketamine treatment will be included along with the fixed intercept. Multiple test corrections (e.g., Bonferroni post hoc tests) will be used to examine differences between levels of significant effects.

The primary outcome measure of the study is the change in fatigue score as measured by the self- reported fatigue instrument.

LIST OF ABBREVIATIONS

ACAT Ability to Consent Assessment Team
ACLS Advanced Cardiac Life Support
AE Adverse Event
AIDS Acquired Immunodeficiency Syndrome
AMPA α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BDNF Brain Derived Neurotrophic Factor
CAT Computer Adaptive Test
CBC Complete Blood Count
CD Clinical Director
CFS Chronic Fatigue Syndrome
CNS Central Nervous System
COI Conflict of Interest
CRF Cancer Related Fatigue
CRIS Clinical Research Information System
CRP C-Reactive Protein
CSRP Committee for the Scientific Review of Protocols
DBP Diastolic Blood Pressure
DSM-5 Diagnostic and Statistical Manual
DSMB Data and Safety Monitoring Board
DSMP Data and Safety Monitoring Plan
EEfRT Effort-Expenditure for Rewards Task
FACIT-F Functional Assessment of Chronic Illness Therapy – Fatigue
FDA Food and Drug Administration
HAM-D Hamilton Depression
HIV Human Immunodeficiency Virus
HRPP Human Research Protection Program
HSP90α Heat Shock Proteins
HSPU Human Subjects Protection Unit
IRB Institutional Review Board
IND Investigational New Drug
IOM Institute of Medicine
LIP Licensed Independent Practitioner
ME/CFS Myalgic encephalomyelitis/Chronic Fatigue Syndrome
MGH- CPFQ Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire
NCCN National Comprehensive Cancer Network
NIH National Institutes of Health
NIMH National Institute of Mental Health
NINR National Institute of Nursing Research
NMDA N-methyl-D-aspartate

1 INTRODUCTION AND BACKGROUND

In primary care settings, 42% of patients are impacted by fatigue; women are affected more frequently than men (Pawlikowska et al., 1994; Ricci et al., 2007; Sharpe & Wilks, 2002). Primary care physicians treat a minimum of one patient with fatigue symptoms for every day of the week (Katon et al., 1991). Yet, fatigue symptoms in 25% of patients go undiagnosed in primary care settings (L. B. Krupp, 2003; Wessely et al., 1999).

Furthermore, fatigue symptoms also negatively affect functioning including quality of life, activities of daily living, employment, and psychological well-being (Hann et al., 1999; Pawlikowska et al., 1994; Robinson et al., 2014).

1.1 FATIGUE IN CHRONIC ILLNESS

Fatigue is one of the most common complaints in chronic illnesses, and many patientsdescribe it as one of the most debilitating symptoms experienced (Arnold, 2008; Eckhardt, et al., 2014; Minnock et al., 2009; Ramsey-Goldman & Rothrock, 2010). In chronic conditions, fatigue impacts up to 67 to 90% of individuals (Fonseca et al., 2014; Krupp etal., 1990; Pollard et al., 2006).

The table below describes the prevalence rates of fatigue reported by individuals with different medical conditions.

Table 1: Fatigue Prevalence Rates in Various Clinical Populations

Disease	Percent Fatigue Reported
AIDS	85%
Cancer undergoing radiation therapy	75-100%
Cancer undergoing chemotherapy	60-90%
Cancer untreated	78%
Parkinson's Disease	60%
Epilepsy	44%
Multiple Sclerosis	97%
Systemic Lupus Erythematosus	85.70%
Rheumatoid Arthritis	70%
Primary Biliary Cirrhosis	64-81%
Post-Lyme Disease	82%
Postoperative Hysterectomy	75%
Remitted Major Depressive Disorder	40%

The fatigue experience of individuals with chronic conditions can be distinguished from ‘normal’ everyday tiredness as being more frequent, unrelenting, unpredictable and unresolved by rest (Dittner et al., 2004; Hewlett et al., 2005). Patients are adamant that fatigue is different from tiredness, because tiredness resolves with rest, but fatigue does not. Fatigue is also described as

extreme fluctuations in lack of mental, physical, and cognitive energy from day to day and throughout each day. Fatigue is often a chronic, unwavering, persistent, disabling problem in patients with chronic conditions. Severe fatigue is reported in up to 57% of patients with single inflammatory rheumatic disease (rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, Sjögren's syndrome, psoriatic arthritis, and scleroderma) and 82% in patients with fibromyalgia (Overman et al., 2016). A recent article revealed that about 35% of cancer survivors complained of disabling fatigue one year after completing cancer treatment and about 25%continue to suffer from persistent fatigue two years or more after completing their treatment (van Leeuwen et al., 2018). Fatigue is one of the most common and debilitating symptom experienced by patients with cancer (Wang, 2008). For myalgia encephalomyelitis/chronic fatigue syndrome (ME/CFS) patients, at least one-quarter of them are house- or bed-bound at some point in their lives (White et al., 1998). Fatigue symptoms for both conditions (cancer survivors and ME/CFS) have significant repercussions for both direct and indirect health economic outcomes (Carlotto et al., 2013;Jason et al., 2008).

ME/CFS often is seen as a diagnosis of exclusion, which also can lead to delays in diagnosis or misdiagnosis of a psychological problem (Fossey et al., 2004; Bayliss et al., 2014). The commonly used diagnostic criteria for ME/CFS is the 2015 Institute of Medicine (IOM) Diagnostic Criteria (Clayton, E.M., 2015). Cancer-related fatigue (CRF)is determined by self-report and there is currently no approved International Classification of Diseases diagnostic criteria/code for CRF.

1.2 MECHANISMS OF FATIGUE

There are several hypotheses that may offer insight into the etiology of fatigue across medical conditions, including in CRF and ME/CFS. The causes and mechanisms of fatigue are complex and multifactorial, and are influenced by somatic, affective, cognitive and psychosocial factors. Below are possible pathophysiological factors underlying fatigue in chronic illness.

1. Autonomic dysfunction: Fatigue is believed to be associated with decreased parasympathetic activity (Koh et al., 2017).
2. Metabolic pathways: A global gene expression analysis of whole blood from a group of patients with chronic illness revealed that high fatigue was associated with differential expression of genes involved in metabolic pathways specifically with actin filaments and migration of cells (James et al., 2015; Pihur et al.,2011).
3. Neurophysiological abnormalities:
    a. Oxidative stress: Fatigue is thought to result from an accumulation of oxidative and nitrosative stress (O&NS), which can induce muscle fatigue, as well as O&NS-induced defects in the sodium-potassium pump, a critical system for neuromotor synaptic transmission (Morris et al., 2016).
    b. Mitochondrial Function: It is also thought that fatigue is associated with mitochondrial dysfunction through the downregulation of the mitochondria lbiogenesis master gene, peroxisome proliferator-activated receptor gamma coactivator 1-alpha, which shifts cellular metabolism to glycolysis causing abuild up of toxic metabolites within monocytes (Morris et al., 2016).
    c. Immune modulatory function: Fatigue is generally associated with a disarray in the concentrations of inflammatory cytokines (Morris et al., 2016; Tripp et al., 2016), which is believed to be a consequence of the activation of the Toll-Like

Receptor Cycle through pathogen-associated and damage-associated molecular patterns, which include heat shock proteins (Morris et al., 2016). One study even showed higher plasma levels of heat shock proteins (HSP90α) with high fatigue compared to those with low fatigue (Bårdsen et al., 2016). A genome-wideepigenetic investigation revealed that pronounced methylation of CpG sites of genes involved in the regulation of immune response and inflammation (e.g., lymphotoxin α) are observed in individuals with high fatigue (Brække Norheim etal., 2016).

Our recent evidence showed that activation of glutamate receptors in T cells mediated the development of chronic fatigue in patients who completed radiation therapy for non- metastatic prostate cancer (Feng et al., 2018). In fact, the activation of glutamate receptor samplified NF-κB activation and inhibition of glutamate receptors reduced pro-inflammatory cytokine production (Feng et al., 2018), suggesting a role of mGluR5 in modulating T cell activation. This proof-of-concept study will use glutamate receptors as a therapeutic target for fatigue. It will provide initial evidence that ketamine relieves fatigue symptoms in individuals across medical conditions. Considering that the action ofketamine on glutamatergic receptors (e.g., NMDA and AMPA) has been identified (Iadarola et al., 2015), findings from this study will be valuable to start confirming the hypothesis mentioned above to further understand the shared mechanism underlying the fatigue experience across medical conditions.

1.3 Current Assessment and Treatment of Fatigue

There are several instruments used to best measure fatigue. Currently, unidimensional and multidimensional scales are sufficient and appropriate measurements to specifically identify fatigued patients. The unidimensional scales measure the physical impact of fatigue and are the most widely used scales (Minton and Stone, 2009). Multidimensional scales are more extensive and can cover anywhere between two and five different aspectsof fatigue but are difficult to use due to time limitations and burden on the patient (Portenoy and Itri, 1999; Minton and Stone, 2009). Objective measures of physical activity and performance (e.g., actigraphy), as well as cognitive function are also used to assess fatigue (Dassouki et al., 2016).

Treatment and management for fatigue symptoms has been attempted by pharmacological and non-pharmacological interventions. No United States (US) Food and Drug Administration (FDA) medication has been approved to treat fatigue, in general. A previous study showed inconsistent results of Rituximab treatment in reducing physical fatigue in Sjögren's Syndrome patients (Arends et al., 2016; Bowman et al., 2017). Erythropoietin, megestrol acetate, psychostimulants, and methylphenidate have been used as anti-fatigue treatments in cancer patients, and showed inconsistent results (Portenoy and Itri, 1999; Mock, 2004). Recent meta-analysis revealed that exercise and cognitive therapy are more effective in reducing cancer-related fatigue than pharmacological agents (Mustian et al., 2017). More investigations to understand the biology of fatigue are warranted to identify optimal therapies for this distressing problem.

1.4 Ketamine as Treatment for Fatigue

We recently observed that ketamine (0.5 mg/kg single intravenous dose) has rapid anti-fatigue effects reported by patients 40 minutes after infusion and lasting until two days post infusion (Saligan et al., 2016). In fact, the effect size of the ketamine-placebo difference was greatest at day 2 (d = 0.59). Figure 1 below describes this anti-fatigue effect of ketamine

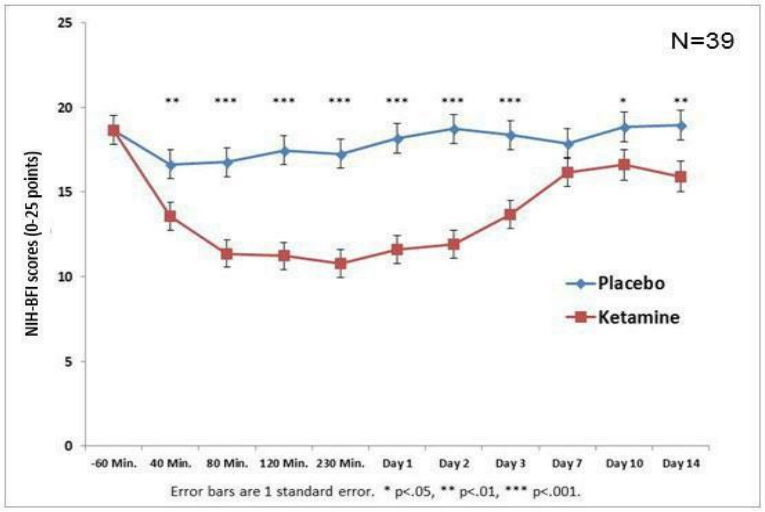


Figure 1 Anti-Fatigue Effects of Ketamine.

This proof of concept study aims to provide initial evidence that a sub anesthetic dose of ketamine has rapid anti-fatigue effects. It will also explore the biologic mechanisms of ketamine's anti- fatigue effects hoping to advance our understanding of the biologic underpinnings of chronic fatigue. Therefore, the information obtained from this study will have several clinical implications both in research and community settings: (1) ketamine, at a low dose, may be effective in rapidly treating fatigue, which can change clinical management for this debilitating symptom; (2) exploring the biologic mechanisms of the anti-fatigue effects of ketamine in this study may reveal pharmacodynamically-active therapeutic targets; and (3) confirmation of the rapid anti- fatigue effects of ketamine may provide opportunities for future exploratory investigations of other long acting anti-fatigue therapies or the anti-fatigue effects of repeated doses of ketamine.

1.5 KETAMINE: RELEVANT PHARMACOLOGY

Initially, ketamine is distributed to highly perfused tissues, including brain, to achieve levels four to five times that in plasma. Ketamine has high lipid solubility and low plasma protein binding (12%), which facilitates rapid transfer across the blood-brain- barrier. The distribution half-life is approximately 10 minutes. Biotransformation of ketamine into multiple metabolites involves N-demethylation by cytochromes p450 to nor ketamine, an active metabolite with a potency approximately one-third that of ketamine. Nor ketamine is then hydroxylated and conjugated to water-soluble compounds that are excreted in urine. Elimination occurs primarily via the kidney, with only a small percentage recovered in the urine as unchanged drug (Chang et al., 1970). The elimination half-life I sapproximately two hours which is secondary to the combination of rapid clearance and large volume of distribution (Domino et al., 1984).

1.6 SAFETY OF KETAMINE ADMINISTRATION

Ketamine is a general anesthetic for human and veterinary use. Ketamine has been administered as an anesthetic to several million adults and children over the last few decades and has a good safety profile. Ketamine exerts sympathomimetic activity and may produce mild to moderate increases in blood pressure, heart rate, and cardiac output. The reported incidence of perceptual disturbances varies from less than 5% to greater than 30%(Knox et al., 1970; White et al., 1980). When such reactions occur, they are usually mild and short-lived (Green and Johnson 1990). No strong evidence exists from long-term studies suggesting that participants exposed to ketamine were at greater risk of abusing iton follow-up. The associate investigator of this study and his team, Dr. Carlos

A. Zarate, Jr. has extensive experience with ketamine, having infused (sub-anesthetic doses) it in patients with treatment-resistant depression under protocol 04-M-0222. This study will continue to use the same dose of ketamine used in the 04-M-0222 protocol, which was found to be safe. Similar exclusion criteria used by 04-M-0222 will be adapted in this protocol to avoid interactions of ketamine with other medications. The lists of medications that participants can take and still be able to safely receive ketamine are listed in Section 3.

1.7 JUSTIFICATION FOR THE ROUTE AND DOSE OF KETAMINE USED

The sub-anesthetic dose of ketamine was selected on the basis of previous published reports describing its safety (Domino et al., 1965; Corssen & Domino 1966; Krystal et al., 1994; Lahti et al., 1995; Krystal et al., 1998; Carpenter, 1999; Krystal et al., 1999; Krystal et al., 2000; Krystal and D'Souza, 2001; Krystal et al., 2002; Krystal et al., 2003a; Krystal et al., 2003b), and its antidepressant effects (Berman et al., 2000; Zarate et al., 2006). We will use the same dose of ketamine, 0.5 mg/kg infused over 40 minutes.

2 STUDY OBJECTIVE

2.1 PRIMARY OBJECTIVE

This study will determine the effect of a single intravenous dose of ketamine (0.5 mg/kg) in reducing clinically significant fatigue in individuals with chronic illness.

Hypothesis: A single intravenous dose of ketamine will reduce clinically significant fatigue in individuals with chronic illness.

2.2 SECONDARY OBJECTIVES

a. To determine the effect of a single intravenous dose of ketamine on symptoms, physical activity, motivation, skeletal muscle strength, and cognitive functioning of study participants.
    i. Hypothesis: A single intravenous dose of ketamine will reduce fatigue-associated symptoms and improve physical activity, motivation, skeletal muscle strength, and cognitive functioning of individuals with chronic fatigue.
b. To determine whether a single intravenous dose of ketamine alters gene expression or the protein levels of pro-inflammatory markers (e.g., lymphotoxin, IFNγ, TNFα) typically seen in fatigue, neurometabolites (e.g., brain derived neurotrophic factor [BDNF], glutamatergic/dopaminergic markers), and mitochondrial markers (e.g., metabotropic glutamate receptors) in the blood.

i. Hypothesis: The change in clinically significant fatigue experienced by individuals with chronic illness after a single intravenous dose of ketamine will be associated with changes in gene expression, levels of pro-inflammatory cytokines, neurometabolites, and mitochondrial markers in the blood. These levels in blood before and after treatment with ketamine or active comparator will also be related to the symptom scores.

As a proof-of-concept study, the selection criteria listed below should not be affected by the heterogeneity of factors that cause fatigue, as described in the introduction. The primary outcome will be assessed by changes in fatigue as measured by the visual analog scale, which will provide initial evidence if the anti-fatigue effects of ketamine is observed across medical conditions. The secondary outcomes of the study will inform the biological underpinnings of this anti-fatigue effect of ketamine, which can advance our understanding of fatigue's etiology.

3 SUBJECTS

3.1 DESCRIPTION OF STUDY POPULATIONS

This protocol will enroll 59 individuals (target n of completers = 50), who are cancer survivors or with chronic illness (e.g., ME/CFS, Sjogren's disease, systemic lupus erythematosus [SLE]) with significant fatigue (Fatigue VAS score of ≥ 50 mm on 0-100 mm horizontal scale). This cut-off fatigue VAS score captured clinically meaningful fatigue experience in other clinical populations, such as in healthy adults (fatigue numeric rating scale [FNS] mean = 5.43 ± 2.26, Kim & Abraham, 2017), those with musculoskeletal diseases (FNS mean = 6.1, confidence interval [5.8, 6.4], Klokkerud et al., 2017), and rheumatoid arthritis (FNS mean = 6.7 +/- 2.1, Minnock, et al., 2009). Drop-outs and participants who withdraw will be replaced to attain the target n = 50 study completers.

3.2 INCLUSION CRITERIA

1. Have chronic, persistent fatigue for at least 6 months;

   a) Intensity = ≥ 50 mm using fatigue VAS (on a 0-100 mm horizontal fatigue scale).

   b) Chronicity = > six months total in the past year using the first item of the revised Piper Fatigue Scale.

2. Be a cancer survivor with a documented medical report of completing primary

cancer treatment > 6 months ago (except hormone and vaccine therapies) OR diagnosed with complex syndromes like ME/CFS, CFS, chronic fatigue, fibromyalgia; OR autoimmune disorder such as SLE, or Sjogren's disease;

3. Able to provide written informed consent;

4. Able to have an accompanying responsible adult for drug infusion study visits;

5. 18 – 70 years of age at the time of signing the informed consent form;

6. Participants may be NIH employees/staff (see below for some exclusion);

7. Individuals of childbearing potential must use adequate contraception, as defined below, prior to study entry and for the duration of study participation. Sexually active subjects must agree to

use at least one medically accepted barrier method of contraception during the study. For example:

- Condoms
- Prescribed hormonal oral contraceptives, vaginal ring, or transdermal patch.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Depot/implantable hormone (e.g., Depo-provera®, Implanon).
- Bilateral tubal occlusion/ligation.
- Sexual abstinence: refraining from intercourse during the entire period of risk associated with the study requirements or if the participant decides to become sexually active during the study, then one of the highly effective birth control methods must be used.

8. Individuals of non-childbearing potential as defined by the following criteria:

- Postmenopausal defined as 12 months of spontaneous amenorrhea or follicle-stimulating hormone (FSH) serum level > 40mIU/mL; appropriate documentation is required.
- Surgically sterile by hysterectomy and/or bilateral oophorectomy with appropriate documentation of surgical procedure.
- Has a congenital condition resulting in no uterus.

OR

- Is sterile
- Has documentation confirming vasectomy

3.3 EXCLUSION CRITERIA

1. Total body irradiation or cranial irradiation for cancer;

2. Has a diagnosis of progressive or unstable disease to any body system causing clinically significant fatigue (e.g., class IV congestive heart failure, end-stage renal disease, liver failure, stage IV chronic obstructive pulmonary disease) including patients with active systemic infections (e.g., human immunodeficiency virus (HIV), active hepatitis, COVID-19 – screened using NIH Clinical Center questionnaire);

3. Individuals with comorbid conditions other than clinically stable cardiovascular, metabolic conditions, and rheumatologic/systemic autoimmune diseases;

4. Current or past psychiatric disorders including medically documented depression with psychosis, bipolar disorder, schizophrenia;

5. Clinically documented post-traumatic stress syndrome and/or traumatic brain injury because of the high risk for ketamine to exacerbate symptoms including hallucinations;

6. Categorized as a high-risk drinker (≥5 drinks/day and ≥15 drinks/week for men, ≥4 drinks/day and ≥8 drinks/week for women). (“Dietary Guidelines for Americans 2015- 2020,” U.S. Department of Health and Human Services and U.S. Department of Agriculture);

7. Detectable alcohol content >1 mg/dL using either breath test or using other biologic samples (e.g., urine);

8. Current substance use disorder within the last five years as diagnosed on the Structured Clinical Interview for DSM-5 (SCID-5) or positive urine toxicology results at enrollment;

9. Participants with clinical hypothyroidism or hyperthyroidism defined by abnormal thyroid stimulating hormone TSH;

10. Poorly controlled hypertension as judged by the Principal Investigator and confirmed by repeat assessment during the screening period (SBP >160 and DBP > 100 in all readings);

11. Any medical condition causing impairment in mobility (e.g., stroke with residual neuromuscular weakness). This may prohibit the assessment of study outcomes, such as physical activity;

12. Any change in dose of regularly scheduled medication or initiation of a new medication (excluding PRN medications) within four weeks prior to signing the informed consent form and throughout the entire duration of the study;

13. Untreated sleep condition.

14. Medically diagnosed kidney disease (except for chronic stable kidney disease with eGFR>45);

15. Medically diagnosed acute narrow-angle glaucoma;

16. Allergic to ketamine, benzodiazepines, flumazenil;

17. With poor IV access;

18. NINR employees or subordinates, relatives, and/or co-workers of NINR employees/staff or study investigators;

19. Pregnant or lactating individuals;

20. Ongoing medical condition that is deemed by the Principal Investigator to interfere with the conduct or assessments of the study or safety of the participant.

21. Taking concomitant medication known to interact with ketamine and/or midazolam 14 days prior to study drug administration and during the study. The medications are shown in the tables below:

List of Psychiatric Medications Allowed and Not Allowed During the Study*

Drug Class	**Episodic Use (as needed)**	**Chronic Use**	**Restrictions**
Antidepressants	No	No	SSRI, SNRI, and serotonin modulators, including Buproprion are allowed if on low maintenance doses, and no history of seizure if taking SNRI.
Antipsychotics	No	No	
Anxiolytics	No	No	
Mood Stabilizers	No	No	

Psychotropic drugs not otherwise specified (including herbal products)	No	No	No drugs with psychomotor effects or with anxiolytic, stimulant, antipsychotic, or sedative properties are allowed.
Sedatives/Hypnotics	No	No	

List of Non-Psychiatric Medications Allowed and Not Allowed During the Study*

Drug Class	Episodic Use (as needed)	Chronic Use	Restrictions
Analgesics	Y	N	Non-narcotic analgesics only
Anorexics (sibuteramine)	N	N	
Antacids	Y	Y	
Antianginal Agents	N	N	
Antiarrhythmics	N	N	
Antiasthma Agents	Y	Y	Systemic corticosteroids are not allowed if
Antibiotics	Y	N	Except erythromycin (see P450-3A4
Anticholinergics	N	N	
Anticoagulants	N	N	
Anticonvulsants	N	N	Carbamazepine, phenytoin, and oxcarbazepine are 3A4 inducers and significantly decrease perampanel levels. Topiramate may increase perampanel
Antidiarrheal Preparations	Y	N	

Drug Class	Episodic Use (as needed)	Chronic Use	Restrictions
Antifungal Agents			
Systemic	N	N	
Topical	Y	Y	
Antihistamines Nonsedating Sedating	 Y N	 Y N	
Antihypertensives	Y	Y	
Anti-inflammatory Drugs	Y	Y[a]	Systemic corticosteroids are not allowed if taking more than > 10 mg /day of prednisone or glucocorticoid equivalent.
Antinauseants	Y	Y	
Antineoplastics	N	N	Agents used in low maintenance doses as immunosuppressive agents (not as anti-neoplastics) such as Azathioprine, Methotrexate, Mycophenolate mofetil, and Belimumab are allowed.
Antiobesity	N	N	
Antivirals	N	N	Except for treatment of HSV with agents without CNSactivity e.g. acyclovir, ganciclovir, famciclovir, valacyclovir

Cough/Cold Preparations	Y	N	Dextromethorphan preps- N/N Guaifenesin - Y/Y Pseudoephedrine - N/N
Diuretics	Y	Yb	
H2-Blockers/ PPI	Y	Yb	Except cimetidine (see P450-3A4 enzyme inhibitorsbelow)
Hormones	N	Yb	Only thyroid hormone replacement, oral contraceptives, and estrogen replacement therapy areallowed.
Hypoglycemic Agents	N	Yb	Only oral hypoglycemic agents are allowed.
Antihyperlipidemics	N	Yb	
Insulin	N	N	
Laxatives	Y	Y	
Muscle Relaxants	N	N	
P450-3A4 enzyme inhibitors	N	N	Including cimetidine, erythromycin, diltiazem, verapamil, ketoconazole, and itraconazole (topical ketoconazole allowed)
Protease Inhibitor	N	N	Including Saquinavir

a Allowed only if being taken prior to enrolling in the study.

b Allowed only if being taken for at least 2 months prior to enrolling in the study and the dose has been stable for at least 1 month.

*Some medications in the above table may be indicated for exclusionary conditions; therefore, it would be unlikely that participants meeting inclusion will be taking them.

4 STUDY DESIGN AND METHODS

4.1 STUDY OVERVIEW

While fatigue is generally a variable phenomenon, we will be enrolling individuals with chronic illness (e.g., cancer survivors and ME/CFS) reporting chronic, persistent, significant fatigue for at least six months. We assume that significant fatigue will persist over the duration of the study. To reduce variability, we will be limiting co-morbid conditions to clinically stable cardiovascular and metabolic conditions.

Therefore, this study will utilize a double-blind (study team and participants will be blinded), active comparator-controlled, cross-over design. This design was used by the original National Institute of Mental Health (NIMH) study (Zarate et al., 2006), where the initial anti-fatigue effects of ketamine were discovered (Saligan et al., 2016). The NIMH study was used to put together the first anti-fatigue ketamine study (15-NR-0037), which was approved by the NIH Combined Neuroscience IRB in 2015. The original study (Zarate et al., 2006) showed that ketamine's antidepressant and anti-fatigue started 40 minutes after ketamine infusion and lasted two days after ketamine infusion (Saligan et al., 2016).

The study will require eight National Institutes of Health (NIH) outpatient clinic visits. In addition, there is a screening visit to determine eligibility and three follow-up phone calls. All tests and study visits will be conducted at the NIH Clinical Research Center.

For participants enrolled in other NIH treatment protocols, when possible, all tests and blood draws will be coordinated around the participant's clinical care procedures so that unnecessary duplication of tests can be avoided and inconvenience to participants is minimized. The procedures involved in all the study time points are discussed in detail below.

4.2 RECRUITMENT

There are ongoing NIH studies that see cancer survivors (e.g., 09-NR-0088), ME/CFSpatients (e.g., 16-N-0058), SLE and Sjogren's patients, that will be some areas to recruit patients for this study. We also hope to enroll non-NIH participants. Flyers (**Appendix 1a**) may be posted on bulletin boards at NIH Clinical Center and in outpatient clinics' waiting rooms. Public service announcements will also be distributed by the NIH CC PRPL/NINR

Communications office through their Facebook/Twitter accounts, PRPL listserv, Research Match, and the NIH newsletter (**Appendix 1b**). Informational cards will also be made available to clinicians and potential participants (**Appendix 1c** and **1d**). There will be no direct solicitation of employees or staff by supervisors or coworkers. It is anticipated that all 59 participants can be recruited in two to three years. Recruitment strategies have been re-evaluated and the study is open to the community as well as NIH patients. Potential participants will be notified about the study through social media posts, email, web postings, newsletters, power point presentations (**Appendix 11**), and educational flyers (**Appendix 12**).

There is currently a shortage of ketamine supply in the NIH Clinical Center (CC) Pharmacy Department. This shortage will not impact the study recruitment but may lengthen the wait time to schedule the first study visit, and the overall duration of the study. We will work closely with the NIH CC Pharmacy Department in scheduling patient visits.

Pre-screening will occur once potential participants inquire about the study. Upon receipt of the inquiry, the research team will perform a phone pre-screening using the pre-screening script (**Appendix 2**). Additionally, potential participants will be asked for their verbal/electronic written permission to allow the research team to access their NIH medical records, if available.

4.3 SCREENING

The participant will be consented prior to any study procedures, including on-site screening. The Ability to Consent Assessment Team (ACAT) will be contacted if there is suspicion that the individual is unable to provide written informed consent. **Appendix 3** will be used to determine eligibility. The screening visit will consist of the following:

1. Fatigue VAS scale. Participants with fatigue VAS score of ≥ 50 mm (on a 0-100 mm horizontal scale) will continue with the study.
2. Revised Piper Fatigue Scale. Participants with fatigue ≥ six months total within a year will continue with the study.
3. About 30 mL of blood will be drawn at the NIH CC laboratory. If results are available for the tests listed below and were collected less-than-a-week before the screening visit (with the exclusion of the pregnancy testing), and the participant

agrees to share with this study (unless indicated below), those values will instead be used.

a. Complete blood count (CBC) w/diff
b. C-reactive protein (CRP)
c. Acute care panel
d. Hepatic panel
e. Thyroid panel (i.e. T3, T4, TSH)
f. Viral markers panel
g. Serum pregnancy testing (may be performed for individuals of child bearing potential if problems arise with obtaining urine pregnancy testing).

4. Urine drug screen (for all potential participants).
5. Alcohol screen by either breath test or using other biologic samples (e.g., urine).
6. Pregnancy testing (for individuals of childbearing potential).
7. A comprehensive clinical assessment by a Licensed Independent Practitioner (LIP), serving as Associate Investigator of the study. The assessment will take approximately one hour and will include measurement of vital signs (including orthostatic blood pressures, anthropometric measurement [waist- to-hip ratio], a detailed medical/social/surgical/psychiatric history, medication review, and physical examination. If a comprehensive clinical assessment by an LIP, who serves as AI of this study, has been done within a month by the referring NIH studies (e.g., CFS phenotyping protocol), this procedure will not be repeated in this study during screening.
8. A review of clinical documentation detailing that the participant has completed treatment (for cancer survivors) or clinical documentation of diagnosis ME/CFS, CFS, chronic fatigue, fibromyalgia), or clinical documentation of diagnosis of SLE or Sjogren's disease.

4.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

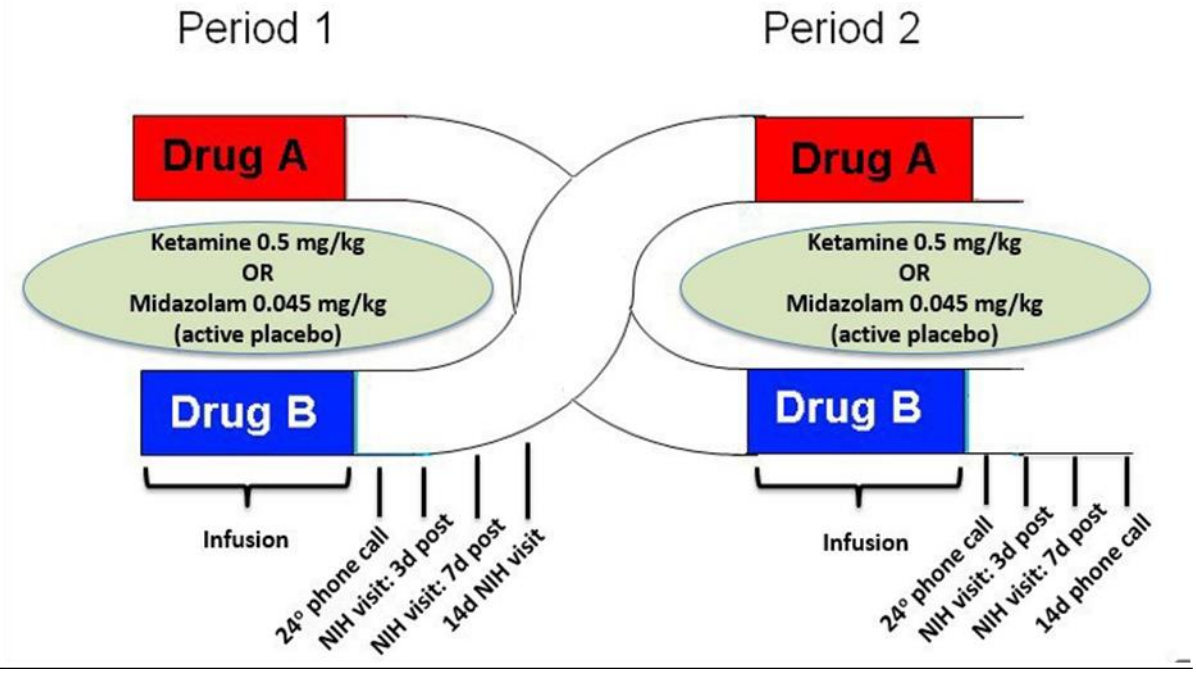
Individuals who do not meet the criteria for participation in this study (screen failure), for example because of a lab value that is out of range may be rescreened at least 6 weeks after returning to their primary treating team. Rescreened participants should be reconsented and will be assigned the same participant number used in the initial screening.

4.5 STUDY PROCEDURES

A copy of the study procedures, including study visits, will be provided to study participants (**Appendix 9** & **10**). To ensure full clinical support at the NIH Clinical Center, study visits will be pre-planned to ensure that the participants' NIH out patient study visits will not fall on the weekends or federal holidays.

The procedures mentioned below will be undertaken at each of the study visits (see **Appendix 4** for Schedule of Events). A previous report confirms the diurnal variability of fatigue, where evening fatigue was observed to be significantly higher than morning fatigue (Dhruva et al., 2013). To account for this variation, all patient-reported outcomes will be collected before the evening time (i.e., before 6pm).

An overview of the study design and procedures is as follows:



4.5.1 Period 1

a) Baseline: A physical examination and review of medical history will be done by LIP and optional safety lab bloodwork, including CBC with Diff and Acute Care Panel, may be drawn, if available lab results are more than a week (7 days) from the infusion visit. Study questionnaires will be completed along with neurocognitive tests, skeletal muscle strength and EEfRT. The physical activity monitor will be given to participants at the end of the visit.

b) Time point #1 (infusion visit): A urine drug and pregnancy test and alcohol screen (with breath test or using other biologic samples) will be administered prior to initiation of infusion. There are optional CBC with Diff and Acute Care panel blood draws, if results from screening labs are more than a week (7 days) from Timepoint 1. Research labs will be drawn throughout the infusion visit. The blinded solutions will be infused through intravenous tubing peripherally or using central ports. Participants will be observed for as long as four hours after study drug infusion (ketamine and active comparator) for cardiorespiratory status and psychosomatic symptoms. After about four hours of observation post infusion, the participant will complete study questionnaires and will be asked if they feel they received ketamine or the active comparator. Participants will be given instructions on their recovery after the drug infusion (Appendix 5).

c) Time point #2: A follow-up phone call will be made within ± 24 hours after Period 1 study drug administration. Participants will be asked about side effects to the study infusion and they will also be reminded to complete the Fatigue VAS.

d) Time point #3: Participants will have an NIH outpatient visit within ± three business days after Period 1 study drug administration. Study questionnaires will be completed along with neurocognitive tests, skeletal muscle strength, EEfRT, physical exam, and blood draw for research blood. Participants will be asked about side effects to the study infusion.

e) Time point #4: Participants will have an NIH outpatient visit within ± seven business days after Period 1 study drug administration. Study questionnaires will be completed along with neurocognitive tests, skeletal muscle strength, EEfRT, physical exam, and blood draw for research blood and safety labs (CBC with Diff and Acute Care Panel). Participants will be asked about side effects to the study infusion.

f) Time point #5: Participants will have an NIH outpatient visit within ± 14 business days after Period 1 study drug administration. Study questionnaires will be completed along with a brief physical exam and a clinical safety labs (CBC with Diff and Acute Care Panel) may be drawn if available lab results are more than a week (7 days) from the infusion visit. Participants will be asked about side effects to the study infusion.

4.5.2 Period 2

a) Time point #6 (infusion visit): A urine drug and pregnancy test and alcohol screen (with breath test or using other biologic samples) will be administered prior to initiation of infusion. Research blood will be collected throughout the infusion visit. For the cross- over phase, the blinded study drug (ketamine or active comparator) will be administered through intravenous tubing peripherally or using central ports over a period of about 40 minutes. Similar to time point #1, participants will be observed for as long as four hours after study drug infusion (ketamine and active comparator) for cardiorespiratory status and psychosomatic symptoms. After about four hours of observation post infusion, the participant will complete study questionnaires and will be asked if they feel they received ketamine or active comparator.

b) Time point #7: A follow-up phone call will be made within ± 24 hours after study drug administration. Participants will be asked about side effects to the study infusion and they will also be reminded to complete the Fatigue VAS.

c) Time point #8: Participants will have an NIH outpatient visit within ± three business days after study drug administration. The study questionnaires will be completed together with the neurocognitive tests, skeletal muscle strength, EEfRT, physical exam, and a research blood draw. Participants will be asked about side effects to the study infusion.

d) Time point #9: Participants will have an NIH outpatient visit within ± seven business days after study drug administration. The study questionnaires will be completed together with the neurocognitive tests, skeletal muscle strength, EEfRT, physical exam, and blood draw for research blood and safety labs (CBC with Diff and Acute Care Panel). Participants will be asked about side effects to the study infusion.

e) Time point #10: A follow-up phone call will be made within ± 14 business days after Period 2 study drug administration. Side effects to the study infusion will be asked and the participants

will be reminded to complete the Fatigue VAS. Participants will return the physical activity monitors by mail.

The blinded study drug (ketamine or active comparator) will be administered by an Advanced Cardiac Life Support (ACLS)-certified, NIH credentialed Clinical Center nurse (all nurses staffed in the Procedure Service Unit of the Clinical Center, where thestudy drug will be administered, are required to maintain an active ACLS certification).The rest of the study outcomes will be administered by members of the research team. Participants will be monitored by research staff present with them at each study time point (i.e., nurse, physicians, and other members of the research team). If at any time during the study, a participant becomes distressed or an emergency situation develops, the research team staff will follow the NIH CC emergency procedures.

4.6 STUDY EVALUATIONS

All questionnaires can be completed by paper-and-pencil and/or directly through password-protected web-based interfaces that can administer both static forms and computer adaptive test (CAT) versions of the questionnaires. These secure web-based interfaces (https://ctdb.nichd.nih.gov/ and https://cdrns.nih.gov/) are developed and maintained in accordance with NIH guidelines by the National Institute of Child Health and Human Development (NICHD) and Center of Informational Technology. Recent studies have shown equivalence in responses between questionnaires answered in electronic and paper/pen formats (Abernethy et al., 2008; Ring et al., 2008).

Descriptions of all study evaluations are below.

4.6.1 Fatigue Assessment:

a) FACIT-Fatigue (FACIT-F) subscale is a 13-item questionnaire that explores fatigue symptoms in various populations, including cancer patients and healthy participants. This questionnaire has shown good test-retest reliability (r = 0.90), internal consistency (α = 0.93 and 0.95) on initial and test-retest administration suggesting that it can be administered as an independent, unidimensional measure of fatigue (Yellen et al., 1997) (~2 minutes).

b) Patient Reported Outcome Measurement Information System (PROMIS) questionnaires are developed from more than 1000 datasets from multiple disease populations including cancer, heart disease, rheumatoid and osteoarthritis, psychiatric conditions, spinal cord injury, and chronic obstructive pulmonary disease. Fatigue, sleep disturbances, depression, and anxiety will be administered by CAT. Initial psychometric properties showed internal consistency reliability coefficient of 0.81 (Hays et al., 2009). These tests will be administered by short form if CAT version is unavailable (~5 minutes).

c) The Fatigue VAS is a 0-100 mm scale. This is widely used to assess fatigue in patients with chronic illness (Segal et al., 2008) (<1 minute).

4.6.1.1 DEPRESSIVE SYMPTOMS ASSESSMENT

a) Hamilton Depression (HAM-D) utilizes a 21-item, clinician-rated paper questionnaire that explores severity of depressive symptoms of the participants in the past week prior to the interview using a Likert scale (0 = none to higher number from 2 to 4 = increasing intensity). When compared to other depression scales, the internal reliability of HAM- D is reported at >0.70 with Pearson's r ranging from 0.82 to 0.98. Retest reliability ranged from0.81 to 0.98; and

it was more sensitive to change than the Beck Depression Scale and the Zung Self-Rating Depression Scale. The total HAM-D score for the 21- item version is obtained by adding the scores from items 1 to 17, as previously described (Sharp, 2015). The predefined cut off score for depression is 15 in a cancer study (Lydiatt et al., 2008), with higher scores indicating higher symptoms of depression. Individuals with higher HAM-D scores (scores above 17) indicating higher symptoms of depression will be referred to a NIH- credentialed psychiatrist for full evaluation. The HAM-D has been utilized to delineate depressive symptoms in cancer- related fatigue studies (Moss et al., 2006; Zhou et al., 2005) (~5 minutes).

4.6.1.2 ASSESSMENT OF COGNITIVE AND PHYSICAL FUNCTIONING

a) Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (MGH-CPFQ) is a brief seven item self-report inventory to assess rates of significant cognitive symptoms, sleepiness, and fatigue in several clinical populations (Fava et al., 2006) (~2 minutes).

4.6.1.3 NEUROCOGNITIVE FUNCTION ASSESSMENT

a) The NIH Toolbox neurocognitive performance tests will use the Dimensional Change Card Sort Test, the List Sorting Working Memory Test and the Pattern Comparison Processing Speed Test (~15minutes).

4.6.1.4 SKELETAL MUSCLE STRENGTH ASSESSMENT

a) Hand Dynamometry – Grip strength will be measured on both hands in a neutral position of the arm, forearm, and wrist. Two consecutive attempts at one-minute intervals will be measured in kilograms with the hand-held dynamometer. Each attempt will require a participant to exert a maximum possible grip force for about five seconds. After a minute of rest, the third attempt will measure fatigue resistance by asking the participant to hold the maximum hand grip as long as able until the 50% maximum grip force (based on the highest maximum hand grip force obtained from the first two attempts) is reached, which is often reached in less than a minute. The test will be repeated on the other hand. The same dynamometer will be used for all participants (~15 minutes).

4.6.1.5 PHYSICAL ACTIVITY ASSESSMENT:

a) Physical activity will be measured daily while participating in the study using a portable physical activity monitor that the participant will wear in their own environment. The monitor can be worn by the participants on their wrists. Data can be extracted during their study visits. (~wear for duration of study participation).

4.6.1.6 MOTIVATION ASSESSMENT

a) The Effort-Expenditure for Rewards Task (EEfRT) is a multi-trial game in which participants are offered a choice between two task difficulty levels for a reward. The task begins with a one-second fixation cross, followed by a five- second choice period in which the participant is informed of the probability of "winning" if the task is completed successfully. Next, the participant either completes 30 button presses in seven seconds with the dominant hand if they have chosen the easy task, or one- hundred button presses in 21 seconds using the non-dominant hand if they have chosen the hard task. Next, the participant receives feedback on whether they completed the task successfully or not. Finally, the participant learns if they have "won," based upon the probability of winning and the successful completion of the task. This task will evaluate

the theory of value-based decision making in the pathophysiology of fatigue by looking for associations in reward and measures of fatigue and motivation in our participants (~20 minutes).

4.6.1.7 BIOLOGIC SAMPLES (PERIPHERAL BLOOD)

Blood will also be drawn for clinical (e.g., CBC and TSH) and research purposes during all NIH clinic visits and will comply with the limits dictated by the NIH ClinicalCenter Medical Administrative Series (MAS) policy on blood draws for research purposes (policy 95-9). No more than a total of 330 mL of blood will be drawn over thecourse of the study.

a) Approximately 30 mL of blood will be drawn from participants at screening (e.g., CBC, TSH) to determine eligibility.

b) Research blood (approximately 90 mL per infusion visit and approximately 30 mL for the outpatient study visits) will be drawn using PAXgene tube and cell preparation tubes to measure changes either in gene expression or protein levels of pro- inflammatory markers (e.g., lymphotoxin, IFNγ, TNFα) typically seen in fatigue, neurometabolites (e.g., brain derived neurotrophic factor [BDNF], glutamatergic/ dopaminergic markers), and mitochondrial markers (e.g., metabotropic glutamate receptors). Mitochondrial markers will be evaluated prior to initial infusion, prior to discharge after the infusion, and during all in person follow-up outpatient visits.

4.6.1.8 KETAMINE ADMINISTRATION

Participants will be administered ketamine (0.5 mg/kg) on either one of the drug infusion study visits. The administration will be by intravenous injection given through an intravenous line over 40 minutes. Participants will be observed for potential side- effects to the study drug.

4.6.1.9 ACTIVE COMPARATOR ADMINISTRATION

To optimize blinding, participants will receive midazolam (0.045 mg/kg) as the active comparator, infused through peripheral IV over 40 minutes on either one of the

drug infusion study visits. This specific dose of midazolam was considered equipotent to

0.5 mg/kg of ketamine, based on a previous study (Murrough et al., 2013). Midazolam was selected based on a report describing its similar pharmacokinetic characteristic as ketamine: fast onset of action and short elimination half-life (Kanto, 1985). In addition, midazolam mimics ketamine's nonspecific behavioral effects (e.g., sedation, disorientation [Gross et al., 1985]). However, the anti-depressant effect of metamine remains distinct when compared with an active placebo such as midazolam (Murrough et al., 2013) or an inactive placebo (Zarate et al., 2006).

4.6.1.10 RANDOMIZATION

Participants will be randomized prior to starting Period 1 of the study. An independent statistician will use a table of random numbers to determine ketamine or active comparator assignment of participants. This is done by choosing a series of randomized numbers corresponding to the number of participants and dividing the series into blocks of four. In each block of four, the two highest would receive ketamine and the two lowest would receive the active comparator. The randomization results will be relayed to the NIH CC Pharmacy before enrolling participants into the study, without divulging the randomization results to the study team. All study participants will be asked a randomization survey (Appendix 7a) after completing the two periods (ketamine and active comparator), to determine whether the participants felt they received ketamine or active comparator. Study staff present during the

infusions will also complete the randomization survey (Appendix 7b) to determine what drug they believe the participants received. This information will be saved with the study outcomes in a secured server and will enable the research team to determine if the study was indeed double-blinded.

4.6.2 End of participation

Participation will end after time point #10. Participants will remain under the care of their own health care providers or referring team during study participation. Clinically relevant data obtained during participation will be shared with participants and their health care providers, with written permission from the participants.

5 MANAGEMENT OF DATA AND SAMPLES

5.1 STORAGE

Blood samples will be stored in secured freezers in the NINR Symptom Management Branch until they are ready for batch analysis. Participants' names and identifying information will be removed and the samples will be assigned codes. The key to the code will be kept in a separate, secure area. Participants will be consented to allow additional analyses of remaining blood samples collected from this study to be used for future experiments.

5.2 DATA AND SAMPLE SHARING PLAN

Research data including results from outcome measures and location of biologic samples will be stored in the NINR-managed databases. These research data can only be accessed in the NIH password-protected websites by study investigators using a two- tiered security process both requiring entry of specific NIH username and password.

Data and samples may be shared with collaborating laboratories at NIH, especially from referring teams (e.g., CFS phenotyping protocols) or with outside NIH collaborators and/or submitted to NIH-designated repositories and databases if consent for sharing was obtained. Repositories receiving data and/or samples from this protocol may be open-access or restricted access.

Samples and data will be stripped of identifiers and may be coded ("de-identified") or unlinked from an identifying code ("anonymized"). When coded data is shared, the key to the code will not be provided to collaborators but will remain at NIH. Data and samples may be shared with investigators and institutions with an FWA or operating under the Declaration of Helsinki (DoH) and reported at the time of continuing review.

Sharing with investigators without an FWA or not operating under the DoH will be submitted for prospective IRB approval. Submissions to NIH-sponsored or supported databases and repositories will be reported at the time of Continuing Review.

Submission to non-NIH sponsored or supported databases and repositories will be submitted for prospective IRB approval.

Required approvals from the collaborating institution will be obtained and materials will be shipped in accordance with NIH and federal regulations.

5.3 RECORDS RETENTION

We will actively protect confidentiality of the participants and the data at each step. All medical records and participant data will be kept confidential and will only be reviewed by the participating investigators. Data will be stored using assigned codes and will be kept in

password-protected computers held at the NINR. Only study investigators will have access to the study data. The participants' names will not appear on any of the data forms. Participants' personal information will be kept as private as possible.

However, records can be inspected by organizations for quality assurance and data analysis. These include the members of the IRB and the NINR Quality Assurance /Quality Control Monitors. Participants' health information will only be disclosed for the purposes of this research study.

5.4 CERTIFICATE OF CONFIDENTIALITY

To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see https://humansubjects.nih.gov/coc/index). As set forth in 45 CFR Part

75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the protocol is managed in compliance with Federal statutes, and regulations. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

6 ADDITIONAL CONSIDERATIONS

6.1 RESEARCH WITH INVESTIGATIONAL DRUGS OR DEVICES

This study has been reviewed by the US FDA and was deemed Investigational New Drug (IND) exempt. The FDA letter is attached in Appendix 8.

7 RISKS AND DISCOMFORTS

The anticipated risks, discomforts and inconveniences of this protocol are those associated with the cognitive tasks, questionnaires and interviews, depression assessment, hand-grip strength testing, phlebotomy, and the ketamine and midazolam infusions.

a) Cognitive Tasks, Motivation Tasks, Questionnaires and Interviews: Responding to questionnaires and tasks entail no medical risk. Some participants may be uncomfortable or anxious answering questions about their illness. Participants do not have to answer any question or perform tasks that make them uncomfortable and can stop the study at any time.

b) Depression Assessment: Results of this assessment that may uncover real-time signs and symptoms of depression will trigger an immediate consultation with the NIMH consult service. Immediate inpatient hospitalization for psychiatric diagnosis will be guided by the findings of the NIMH consult service. Results of the consultation will be discussed with the participant and

with his/her consent, the health care providers will be informed. Referral with the NIMH clinical consult team will be arranged.

c) Skeletal Muscle Strength Testing: Minimal discomfort might be experienced during skeletal strength tests (e.g., hand muscle soreness) which often lasts less than 5 minutes.

d) Phlebotomy: Needle punctures for drawing blood may cause pain and carries a small risk of bleeding, bruising, discomfort and/or infection at the injection site, or temporary dizziness. The participants will be monitored for about 15 minutes after their blood drawing to assess and treat any complication related to the procedure.

e) Ketamine: This is a general anesthetic for human and veterinary use. Ketamine has been administered as an anesthetic to several million adults and children over the last few decades and has a good safety profile. Ketamine exerts sympathomimetic activity and may produce mild to moderate increases in blood pressure, heart rate, and cardiac output. Participants may also experience central nervous system (CNS) effects such as hallucinations, scary thoughts, paranoia, or sedation. Since ketamine is given by infusion over 40 minutes, the likelihood for CNS effects to occur is reduced. If they occur, they often last for an hour after administration. For safety purposes, the study design used in this protocol is the same design used in the original NIMH study (Zarate et al., 2006). That study observed that adverse reactions from ketamine (e.g., perceptual disturbances, confusion, elevations in blood pressure, euphoria, dizziness, and increased libido) ceased within 80 minutes after the ketamine infusion and none of these adverse reactions persisted beyond 110 minutes. Ketamine is generally considered unsafe for use during pregnancy and breast-feeding. Please see section 1f of the protocol introduction for further discussion on the safety of ketamine.

f) Midazolam: This is widely used, short-acting benzodiazepine and anesthetic agent used in adult and pediatric populations. It will be used as the active comparator in this study. A recent study (Murrough et al., 2013) reported that up to 4 hours after midazolam infusion, the most common adverse reactions include generalized malaise, dizziness, headache, restlessness, nausea or vomiting, dry mouth, decreased energy, and poor coordination. There were drops in blood pressure noted, but it resolved 240 minutes after infusion. Participants will be closely monitored during infusion and during the entire study. Management of side effects and emergency plan to handle adverse events are discussed below. Because of the sedative effect of ketamine and midazolam, participants are required to have another adult individual drive them home. The research team will provide transportation for study participants without a means of transportation, to take the participant with an accompanying responsible adult home after the infusion visits.

g) Physical Activity Monitor: Minimal medical risk. Participants will be informed that they may refuse to perform a test or to stop a test at any time and for any reason.

h) Based on the insert packages for both agents, aside from the adverse reactions mentioned above, these common adverse reactions from both the study drugs are also expected: Sore throat, eye pain, bad taste in mouth, increase in saliva and/or drooling, mood changes, confusion, unusual headache, tingling or “pins and needles”, itching or rash, weakness.

8 SUBJECT SAFETY MONITORING

8.1 STUDY DRUG ADMINISTRATION MONITORING:

Infusion, patient monitoring, and patient discharge will comply with the criteria and procedures dictated by NIH Clinical Center Medical Administrative Series (MAS) policy on administration of sedation (policy 92-9). Participants are closely monitored (continuously with telemetry, blood pressure, respiration, oxygen saturation) for potential study drug reactions during the 40-minute infusion of ketamine or midazolam, and additional 40 minutes post infusion. Participants will continue to be monitored (blood pressure, respiration, heart rate, oxygen saturation) for a maximum of 4 hours. Participants will be discontinued from the study if they develop manic, psychotic, or other symptoms that require treatment with medications.

A clinician with advanced medical training (i.e., physician or nurse practitioner trained in ACLS and conscious sedation of anesthetic agents (i.e., ketamine and midazolam) will be present throughout the administration of study drugs so that adverse reactions can be evaluated and treated promptly. Medications such as flumazenil would be given at a clinically indicated dosing regimen if a patient were to experience serious anxiety, agitation, or other untoward effects. Anti-nausea medications may also be given for other study drug side effects. A fully equipped emergency medical cart is located nearby in the unlikely case of an untoward reaction or development of another health- related problem. Some evidence suggests that excessive noise and stimulation during recovery from sedation might be associated with emergence reactions (or psychotomimetic effects). Thus, the study drugs will be administered in a well-monitored location with muted lighting, noise, and physical contact. Prior to discharge, participants will be evaluated and confirmed to meet discharge criteria as described in MAS policy 92- 9.

Adverse event assessments will be conducted during each study time point. For events that occur at the NIH and require immediate medical attention, procedures will be instituted at NIH or at a local hospital Emergency Room as deemed appropriate. With the patient's consent, their treatment teams and healthcare providers will also be informed.

Participants may withdraw from this study for any reason at any time without penalty or prohibition from enrolling in other NIH protocols for which they are eligible. Participants who, in the opinion of the PI and in consultation with the MAI, have an event that would make it unsafe to continue participation may skip or delay measurement of a specific study procedure, or be withdrawn from the study.

Reasons for withdrawing a participant from the study at any time include:

a) Clinically significant abnormal lab tests (e.g., absolute neutrophil count <1.5Kcells/μL, platelet

<75K cells/μL, hemoglobin <9 g/dL).

b) PI's decision that it would be unsafe for the individual to continue participation(decision made in consultation with the MAI).

c) Withdrawal of consent and/or participant decision.

d) Psychotic, manic, or other symptoms that require pharmacological treatment. Data Collection of Adverse Events

Not clinically significant and expected mild to moderate symptoms as listed in the risk section and safety labs will not be collected as AEs.

9 OUTCOME MEASURES

9.1 PRIMARY OUTCOME MEASURES

The primary outcome measure of the study is the percentage change in self-reported fatigue VAS score before and 3 days after receiving ketamine or active comparator. A 20% change in fatigue VAS score 3 days after ketamine treatment will be considered indication of efficacy in this study.

9.2 SECONDARY OUTCOME MEASURES

The secondary outcomes of this study include: symptoms, physical activity count, skeletal muscle strength, motivation score, cognitive function test scores, gene expression or protein levels of pro- inflammatory markers (e.g., lymphotoxin, IFNγ, TNFα), neurometabolite (e.g., BDNF) levels, and mitochondrial markers (e.g., metabotropic glutamate receptors) before and after a dose of ketamine or active comparator at multiple time points.

Missing data from either primary or secondary outcomes will not be used in the data analysis for that particular variable but will be included in the discussion of results.

10 STATISTICAL ANALYSIS

10.1 ANALYSIS OF DATA/ STUDY OUTCOMES

This is a double-blind, active comparator-controlled, cross-over study. The primary outcome measure will be the percentage change in fatigue scores (the difference between day 3 score minus the baseline score, divided by the baseline score) before and at 3rd day after a single intravenous dose of ketamine or active comparator.

All statistical analysis will be conducted using available statistical software (e.g., SPSS and/or SAS). Significance will be evaluated at $p<.05$, two-tailed, unless otherwise stated. The Kolmogorov-Smirnov test will be used to examine whether the distribution of the outcome measure is normal. If the data are not normally distributed, transformations will be used to improve the fit. Carryover effect will be tested between AB vs. BA groups to see if there's any statistical difference between the two groups. The difference of primary outcome (mean VAS percent changes) of ketamine (μA) and active comparator (μB) will be tested between the AB and BA sequence arms. If there's a carryover effect, then each phase should be tested separately.

10.2 ANALYSIS OF SECONDARY ENDPOINTS

Secondary analysis will also examine the percentage change in fatigue symptoms, determined by comparing fatigue VAS scores prior to ketamine infusion and multiple time points after ketamine infusion. A linear mixed model with restricted maximum likelihood estimation will be used to examine changes in fatigue symptoms over the course of the trial where all participants with at least a pre-infusion and one post-infusion measure will be included. Within-subjects factors will include time with pre-infusion and all other points. The interaction between time and ketamine treatment will be included along with the fixed intercept. The random intercept and a random effect for subject will be included if they are a significant addition to the model.

The effect of ketamine on VAS will also be tested by the binomial response outcome determined at 3-day post infusions. Clinical response will be determined by the proportion of change in VAS from pre-treatment to 3-day post treatment. Participants achieving 20% reduction or more between pre-infusion and day 3 will be considered responders. The proportion of responders in each clinical population will be compared using McNemar's Test. Symptom evaluation will be conducted at the end of each study period (Periods 1 and 2) to determine who experienced a

clinical response. As exploratory analyses, other methods to determine efficacy, such as a 20-point difference from pre- infusion to 3-day post study drug infusion and number of participants reaching 40- point mark in the fatigue VAS post study drug infusion will be investigated. Group comparisons of primary and secondary objectives will not be done using raw scores, but by the percentage change of each variable, pre and post treatment.

The scores and levels of the other secondary outcomes (symptoms, physical activity count, skeletal muscle strength [e.g., maximum voluntary contractions], motivation score, cognitive function test scores, changes in gene expression or protein levels of pro- inflammatory markers, neurometabolite [e.g., BDNF] levels, and mitochondrial markers (e.g., glutamate receptor 4) will be compared using linear mixed model from prior, during, and after ketamine or active comparator infusion. The significance level may be adjusted using a Bonferroni approach based on the number of secondary measures examined with the linear mixed model.

10.3 POWER ANALYSIS

The primary aim of the study is to determine the effect of a single intravenous dose of ketamine (0.5 mg/kg) in reducing clinically significant fatigue in individuals with chronic illness, not on specific clinical populations. The anti-fatigue effect of ketamine will not be examined by clinical subgroup, but as an entire fatigue cohort with chronic illness.

Since there is no previous ketamine study that used mixed model analysis measuring fatigue or other behaviors using the VAS, we estimated our sample size using a simple AB/BA crossover design, ignoring any covariates.

The sample size estimate for the primary outcome is estimated by McNemar's exact conditional test. If we estimate the discordant subject ratio to be 3:1, for example, the portions for response discordant subjects to be 0.45 for p10 (success for ketamine, failure for active comparator) and

0.15 for p01 (failure for ketamine, success for active comparator), at significance level of 0.05, with expected power of 0.8, two-sided probability, the estimated number of participants required is 50. We anticipate a 15% drop out rate so the total number of participants to be recruited is 50 + 09 (drop out) = 59. We estimate to enroll 1-2 participants per month; hence, it will take about 2 – 3 years to accrue 59 participants.

10.4 INTERIM ANALYSIS FOR EFFICACY

We plan an interim analysis of the participants who completed the study to answer the primary aim of the study: to determine the effect of a single intravenous dose of ketamine (0.5 mg/kg) in reducing clinically significant fatigue in individuals with chronic illness. The results of the interim analysis will guide in the planning for the next phase of the unit's research program. So, it is requested that the study be unblinded for the Primary Investigator and other investigative staff to make a decision to discontinue the trial due to superiority or to continue the trial.

The primary endpoint used for this analysis is the percentage of change in Fatigue Visual Analog Scale (VAS) scores. Change in fatigue VAS scores will be through comparison of fatigue VAS scores collected at the first visit (Baseline) and the third visit (3 days after study drug infusion) during each treatment arm (Ketamine, active comparator). For each participant, the difference in fatigue VAS score during the ketamine as well as the active comparator arm will be calculated. A 20% decrease in the fatigue VAS score is the predetermined primary outcome will be considered the indication of efficacy in this analysis. The hypothesis that fatigue VAS Diff = 0

will be tested by means using appropriate methods such as the student's paired t-test using appropriate normal approximations. A p-value < 0.05 will be considered statistically significant.

Besides the normality assumption for the paired t-test, the analysis of objectives makes two main assumptions: absence of period effect and no treatment-period interactions. A test for period effect will be performed by comparing the mean differences of the fatigue VAS scores for the two treatments orders (under the hypothesis that the difference is equal to 0, no period effect). If there is evidence for a period effect (p-value < 0.05), the results will be adjusted. The interaction between treatment and period will be examined by comparing the average of the fatigue VAS scores within patient between the two treatments of the First and Second Periods. If the interaction between treatment and period is significant (p-value < 0.05) only the first period will be used.

Missing data values will be handled by using multiple data imputations. If available, baseline measurements at the beginning of each treatment period (First and Second Periods) would be included as covariates in the analysis. Analysis will be performed using the available software SPSS Statistics (IBM, New York, USA) or SAS (SAS Institute Inc., Cary, NC, USA).

11 HUMAN SUBJECTS PROTECTION

11.1 SUBJECT SELECTION

Accrual will be equitable for this study. Participants will be included regardless of race and ethnicity. Both women and men will be enrolled in the study because fatigue is not a gender-specific experience. Participants with active psychotic symptoms will be excluded from this study.

11.2 JUSTIFICATION FOR EXCLUSION OF CHILDREN

Participants younger than 18 are excluded as fatigue in adults differs from that in children. In addition, there are no studies available showing consistent data on the dose, pharmacokinetics, antidepressant efficacy and safety of ketamine in children with IV infusion.

11.3 JUSTIFICATION FOR EXCLUSION OF OTHER VULNERABLE SUBJECTS

11.3.1 Pregnant and lactating individuals:

Will be excluded. Ketamine is generally considered unsafe for use during pregnancy and breast-feeding. Study participants will be reminded of this risk and will be encouraged to use appropriate birth control methods.

11.3.2 Impaired consent capacity:

Will not be included. Individuals who are not capable of giving their own informed consent will not be eligible for this study since study procedures will require participants to understand verbal and written questions and instructions. If necessary, consultation to assess consent capacity will be obtained from the NIH Ability to Consent Assessment Team (301-496-9675).

NIH staff:

May be included. With no scientifically based reason to exclude NIH employees/staff, we can offer the opportunity for this group to participate in this study if interested and eligible.

Other vulnerable subjects:

Fatigue is a very common symptom of HIV+ patients even those who are optimally treated with highly active anti-retroviral treatment (Andersen et al., 2006). Furthermore, it has been shown that increased levels of pro-inflammatory cytokines are found in the central nervous system of HIV+ individuals (Tyor et al., 1992). To limit this variable, this study will exclude patients who are HIV+. Individuals who are not capable of giving their own informed consent will not be eligible for this study since study procedures will require participant to understand verbal and written questions and instructions. There is also strong evidence showing that ketamine, especially at higher doses can exacerbate psychotic symptoms. To avoid this, individuals with active psychotic symptoms are excluded from this study.

11.4 JUSTIFICATION OF SENSITIVE PROCEDURES

11.4.1 Active comparator arm:

By using an active comparator, we will be able to expose the fewest participants to experimental conditions to know whether a rapid anti-fatigue response can be achieved with a single intravenous dose of ketamine. An active comparator condition would help us interpret study results limiting patient bias.

11.4.2 Drug and alcohol-free period:

Participants will be free of illicit drug and alcohol for two weeks prior to ketamine administration and during the study. This drug- and alcohol-free period was chosen to reduce the risk of a carry- over effect. Such a carry-over effect from previous treatments could make study results difficult to interpret.

11.5 SAFEGUARDS FOR VULNERABLE POPULATIONS

Participants with psychotic symptoms during screening will be referred immediately to the NIMH consult service.

11.5.1 Requirement of a primary care provider for study participation:

The study will not provide any clinical care and it will not diagnose any clinical conditions. Any study-related clinical findings will be relayed to the primary care provider for further evaluation and management.

11.5.2 NIH staff:

All participants will be asked if they are an employee of NIH during screening. NIH staff will not be solicited for participation but will not be excluded if they express the desire to enroll. Protections for employees and staff participating in this study include: 1) assuring that the participation or refusal to participate will have no effect, either beneficial or adverse, on the participant's employment or position at NIH, 2) giving employees and staff who are interested in participating the "NIH Information Sheet on Employee Research Participation" prior to obtaining consent (see Appendix C from OHSRP SOP 14f), and 3) assuring that there will be no direct solicitation of employees or staff. Employees that participate in this protocol during work hours will be informed that they must obtain their supervisor's permission and that per NIH guidelines they will not be paid (as described in section 23).

To ensure that research staff are adequately trained to respect the privacy and confidentiality of NIH employees/staff, study investigators and staff are required to complete the CITI "Just in Time" Training: Vulnerable Subjects – Workers/Employees. In addition, all study investigators

and staff who have contact with study participants or who have access to medical records will be required to complete the mandatory "NIH Clinical Center Patient Confidentiality and Privacy" training at the start of their employment and annually thereafter. These trainings must be completed prior to study investigators and staff having contact with participants and/or personally identifiable information (PII).

12 ANTICIPATED BENEFIT

This protocol offers no direct benefit from participation. Previous result from a placebo-controlled study found that ketamine was effective in the short-term for treatment of major depressive disorder and bipolar disorders (Zarate et al., 2006). Findings from this proposed study may provide generalizable knowledge about developing new treatments for fatigue.

13 CONSENT DOCUMENTS AND PROCESS

13.1 DESIGNATION OF THOSE OBTAINING CONSENT

Study investigators designated as able to obtain consent, per the study personnel page, will obtain informed consent. Only associate investigators who are licensed independent professionals and credentialed to prescribe medications in the NIH Clinical Center (e.g., MDs, NPs) are designated to obtain informed consent for this study. All study investigators obtaining informed consent have completed the NIMH Human Subjects Protection Unit (HSPU) "Elements of Successful Informed Consent" training.

13.2 CONSENT PROCEDURES

All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures and potential risks of the study and of their rights as research participants. They will be informed that they may withdraw from the study at any time without prejudice to themselves. Participants will have the opportunity to carefully review the written consent form and ask questions regarding this study prior to signing. The PI will sign the consent form. The original consent form will be filed with NIH Medical Records. A copy of the completed signed consent will be provided to the participant.

Consent Process by Telephone/NIH-Approved Telehealth Platform/iMED

Informed consent will be obtained per the Clinical Center Policy and Communication Bulletin MAS policy M20-1 and IRB Policy 303. Subjects will be provided a copy of the consent for review. Subjects will be given ample time to read and review the consent before the appointment for the formal informed consent process and signing. Subjects will choose the location for the telephone/telehealth informed consent process, but the research team will highly encourage the subjects to choose a location that will private, quiet, and have the remote possibility of interruptions. Subjects will be contacted either by telephone or NIH-approved telehealth platform and the non-investigational nature of this trial, the associated assessment and test options, biological sample collection, and attendant risks and discomforts will be carefully explained to the subject.

The subject will sign and date either the paper informed consent or use electronic signature (e-sign) using the CC approved platform or method (iMED).

If electronic signatures will be used, the study team plans to use the CC approved platform, currently iMED consent, to obtain electronic signatures. The identity of participants will be

verified by asking them to state their full name and date of birth. The electronic signatures will be obtained "synchronously and in real-time" whether it is in-person, telephone, or telehealth consent. iMED consent will capture electronic signatures via the methods listed below:

- Using a smartphone: participants will be registering their signatures using their finger. Participants will receive a secure link that leads them to secure "web pages" that will capture their electronic signatures using their finger.
- Using a computer/tablet/laptop: participants will be registering their signatures using a computer mouse or their finger/stylus (for touch/stylus enabled tablets and computer screens). Participants will receive a secure link that leads them to secure "web pages" that will capture their electronic signatures using the aforementioned methods.

Signed paper copies of consent will be returned via fax, mail, or secure e-mail to the consenting investigator to be signed and dated. A fully executed copy of the consent will be available in the participant's research record. Consent forms signed using the CC approved electronic signature platform (iMED consent) will be archived and stored in the participant's research record via an automatic secure electronic transmission immediately after all the required signatures are obtained. All participants will be provided with a copy of the fully executed consent (paper copy by mail or electronic copy by secure electronic methods based on participant's preference). The informed consent process will be documented in the medical record, including the name of the interpreter.

13.3 CONSENT DOCUMENTS

The consent form contains all required elements.

14 DATA AND SAFETY MONITORING

14.1 DATA AND SAFETY MONITOR

Data and safety will be monitored primarily by the NIMH-IRP Data and Safety Monitoring Board (DSMB).

14.2 DATA AND SAFETY MONITORING PLAN

The data and safety monitoring plan (DSMP) of the study includes monitoring by the NIMH-IRP DSMB. The DSMB will meet every 4-6 months to review study accrual and progress, adverse events related to the study, and safety and outcome data. Specific data elements required by the DSMB will be established at the first meeting the protocol is reviewed. The DSMB will have the authority to require changes in the study design, or to stop all or part of any study based on accumulating safety data. The PI will prepare a report to the DSMB on a semi-annual basis or as requested by the board.

The PI will also be responsible for monitoring data and safety. Issues of participant recruitment, participant enrollment, data collection, data storage, and other safety events will be reported to the PI every week by the research staff. Involved associate investigators (AIs) will be informed about these issues on a quarterly established schedule.

The medically responsible investigator has the authority to break the blind in the event of an emergency. Breaking of the blind, life threatening injury or death all require immediate reporting to the DSMB and the NINR Clinical Director. A written notification to the DSMB chair must

follow within 7 days. Specific requirements for data safety monitoring will abide by the document entitled "Standard Operating Procedures for the NIMH IRP Data and Safety Monitoring Board."

14.3 CRITERIA FOR STOPPING THE STUDY OR SUSPENDING ENROLLMENT OR PROCEDURES

As no SAEs are anticipated, the study will temporarily cease enrolling new patients if any potentially related SAEs occur, until the PI and the IRB determine there is no risk to continuing. Other investigators will consult with the PI if they believe that such actions are warranted to protect the safety, welfare or rights of subjects or to protect data integrity. The PI and the NINR CD may also recommend temporarily suspending or closing enrollment or stopping the study at any time due to safety concerns or slow recruitment.

15 QUALITY ASSURANCE (QA)

15.1 QUALITY ASSURANCE MONITOR

The quality assurance of the study will be monitored by a QA monitor, who is independent of the study.

15.2 QUALITY ASSURANCE PLAN

This is a more than minimal risk study. Per the NINR quality assurance policy, this study will be monitored after enrollment of the first participant, annually thereafter, and at close-out. Ad hoc monitoring visits may be scheduled per the request of the study team, the independent monitor, or NINR Clinical Director.

16 REPORTING OF UNANTICIPATED PROBLEMS, ADVERSE EVENTS AND PROTOCOL DEVIATIONS

The Principal Investigator is responsible for detecting, documenting, and reporting unanticipated problems, AEs, including SAEs and deviations in accordance with NIH Policy 801. Relatedness to the research of all SAEs will be determined by the PI in consultation with the NINR CD and the Medical Advisory Investigator for the study.

17 ALTERNATIVES TO PARTICIPATION

There is no FDA-approved medication to treat fatigue. Aside from activity enhancement, National Comprehensive Cancer Network (NCCN) guidelines recommend psychosocial improvement, attention-restoring therapy, nutrition, and sleep to manage fatigue. NCCN further recommends the use of psychostimulants to manage fatigue once other causes (e.g., anemia, sleep disorders) are ruled out. The effectiveness of these recommended interventions has not been validated in large clinical trials.

18 PRIVACY

All research activities will be conducted in as private a setting as possible.

19 CONFIDENTIALITY

19.1 FOR RESEARCH DATA AND INVESTIGATOR MEDICAL RECORDS

The information obtained from participants will be stored electronically and in paper files in a secure location at the NIH CC. Hard copies will be kept in double-locked storage. Electronic

records will be stored in password protected files on secure servers at the NIH. The information will be kept private. Only study staff will have access to the information.

19.2 FOR STORED SAMPLES

Blood samples will be dated (date of collection) and stored using codes that the research team will assign in locked NINR Laboratory of Symptom Management freezers until they are analyzed. Only study investigators will have access to the stored samples collected in this study.

19.3 SPECIAL PRECAUTIONS

Data will be kept in password-protected computers. Hard copy data/records are stored in a locked cabinet in a room in NIH CC that is locked when unoccupied. Research data including results from outcome measures and location of biologic samples will be stored in the Clinical Trials Database (CTDB) and Common Data Repository for Nursing Science (cdRNS). These web-based applications are compliant with NIH privacy and confidentiality requirements and policies. Only study investigators will have access to stored data collected in this study. De-identified results from this study will be posted on clinicaltrials.gov.

20 CONFLICT OF INTEREST

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NINR has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

21 TECHNOLOGY TRANSFER

There are no transfers or agreements to report.

22 RESEARCH AND TRAVEL COMPENSATION

Participants will be compensated for research-related inconveniences. Compensation will be prorated for parts completed if participants do not complete the study. Payments will be sent after each visit. The schedule for procedure-based payments is below:

**EEfRT: compensation up to $20 based on the participant's EEfRT score per visit.

Period 1 Baseline Visit	**Payment**
Blood draw	$10
Questionnaires (all)	$20
Cognitive/Psychological Testing (HAM-D, Hand Strength, NIH Toolbox)	$20
Total before EEfRT	$50
**EEfRT up to $20	Up to $20
Total with EEfRT	$70
Period 1 Infusion 1	**Payment**

Blood Draw – Serial/Sampling through IV	$100
Heparin Lock insertion (per attempt)	$10
Questionnaire (VAS x 5, 6 questionnaires, randomization, AE assessment, HAMD)	$40
Total	$150
Period 1 Telephone call follow-up	**Payment**
Telephone Follow-up/Interview	$10
Period 1 Follow-up Visit (+/- 3 days)	**Payment**
Blood draw	$10
Questionnaires (all)	$20
Cognitive/Psychological Testing (HAM-D, Hand Strength, NIH Toolbox)	$20
Total before EEfRT	$50
**EEfRT up to $20	Up to $20
Total with EEfRT	$70
Period 1 Follow-up Visit (+/- 7 days)	**Payment**
Blood draw	$10
Questionnaires (all)	$20
Cognitive/Psychological Testing (HAM-D, Hand Strength, NIH Toolbox)	$20
Total before EEfRT	$50
**EEfRT up to $20	Up to $20
Total with EEfRT	$70

Period 2 Baseline Visit	**Payment**
(Optional) Safety Blood draw	$10
Questionnaires (all)	$20
Total up to	$30

Period 2 Infusion 2	**Payment**
Blood Draw – Serial/Sampling through IV (research blood x 5)	$100
Heparin Lock insertion (IU per attempt)	$10
Questionnaire (VAS x 5, 6 questionnaires, randomization, AE assessment, HAMD)	$40
Total	$150

Period 2 Telephone call follow-up	**Payment**
Telephone Follow-up/Interview	$10
Period 2 Follow-up Visit (+/- 3 days)	**Payment**
Blood draw	$10
Questionnaires (all)	$20
Cognitive/Psychological Testing (HAM-D, Hand Strength, NIH Toolbox)	$20
Total before EEfRT	$50
EEfRT up to $20 **Total with EEfRT	Up to $20 $70
Period 2 Telephone call follow-up	**Payment**
Telephone Follow-up/Interview	$10

Total payment at the end of Period 2 = $340

Total payment entire protocol = $710

This study will offer reimbursement or payment for meals and other reimbursements, on a case-by-case basis, based on NIH guidelines.

The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, participants are not paid for taking part in research studies at the National Institutes of Health. Payment will be sent after each visit. The Institute can pay or reimburse car mileage based on the Government reimbursement rate. There will not be prorated compensation.

NIH employees and staff who participate during work hours must have permission from their supervisor. NIH employees or staff must either participate outside of work hours or take leave in order to receive transportation assistance.

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24 ATTACHMENTS/APPENDICES

Appendices are uploaded to iRIS.
Appendix 1a: Recruitment Flyer
Appendix 1aa: Recruitment Flyer for Clinics
Appendix 1b: Public Service Announcements
Appendix 1c: Informational Cards for Clinicians and Investigators Appendix 1d: Informational Cards for Participants
Appendix 2: Phone Pre-Screening Script Appendix 3: Eligibility Checklist Appendix 4: Schedule of Events
Appendix 5: Post Infusion Discharge Instructions Appendix 7a: Randomization Survey (Participants) Appendix 7b: Randomization Survey (Study Team) Appendix 8: FDA Letter
Appendix 9: Visit Schedule Appendix 10: Monthly Schedule
Appendix 11: Recruitment Power Point Presentation Appendix 12: Educational Flyer
Appendix C: NIH Information Sheet on Employee Research Participation