UNIVERSITY OF UTAH
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TREK: Ketamine-assisted Psychotherapy (KAP) for Patients with Existential Distress associated with Non-operable GI Cancers

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DOCUMENT HISTORY

Document	Date	Overall Rationale
Original Protocol	21JUL2023	Not applicable
Amendment 1	09FEB2024	Updated eligibility criteria, removed MQOL questionnaire, and updated questionnaire time points

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study 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 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. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

ABREVIATIONS

Abbreviation	Definition/Explanation
ACI	As clinically indicated
AE	Adverse event
ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AV	Atrioventricular
BCVA	Best-corrected distance visual acuity
BICR	Blinded Independent Central Review
β-HCG	Beta-human chorionic gonadotropin
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CL_{cr}	Creatinine clearance
C_{max}	Maximum observed concentration
C_{min}	Trough observed concentration
CMP	Comprehensive metabolic panel
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CYP	Cytochrome P450
CQ	Chloroquine

Abbreviation	Definition/Explanation
DILI	Drug-Induced Liver Injury
DoR	Duration of Response
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ECG	Electrocardiogram
Eg	Exempli Gratia (for example)
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyltransferase
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
i.e.	Id est (that is)
IEC	Independent ethics committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional review board
LDH	Lactate dehydrogenase
MRI	Magnetic resonance imaging
NIH	National Institute of Health
KAP	Ketamine-assisted Psychotherapy
PD	Pharmacodynamic(s)
PDAC	Pancreatic Ductal Adenocarcinoma
PFS	Progression-Free Survival
PK	Pharmacokinetic(s)

Abbreviation	Definition/Explanation
PO	Per os (administered by mouth)
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QTc	QT interval corrected
QTcF	QT interval corrected using Fredericia equation
RBC	Red blood cell
RP2D	Recommended Phase 2 Dose
SAE	Serious adverse event
SD	Stable disease
SD-OCT	Spectral-domain ocular coherence tomography
$T_{1/2}$	Terminal elimination half-life
TdP	Torsades de Pointes
T_{max}	Time of maximum observed concentration
ULN	The upper limit of normal
VF	Visual field
WBC	White blood cell

1 PROTOCOL SUMMARY

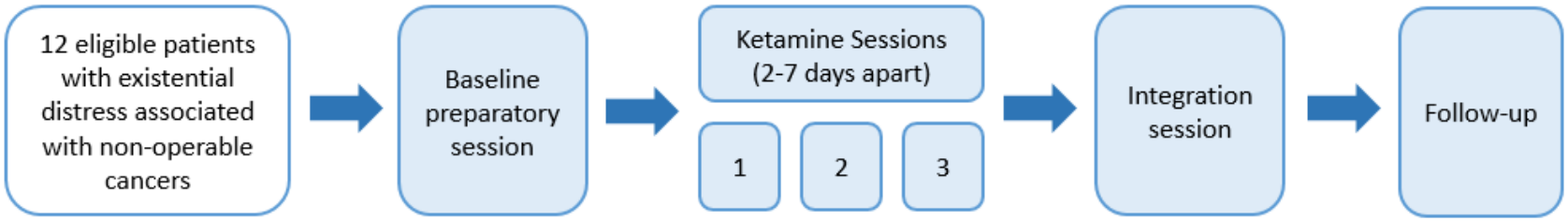
1.1 Synopsis

Title:	**TREK**: Ketamine-assisted Psychotherapy (KAP) for Patients with Existential Distress associated with Non-operable GI Cancers
Protocol Short Title	TREK
Study Description:	Open label, Pilot
Phase:	Pilot
Objectives:	**Primary Objective:** To assess the feasibility of recruiting, consenting, enrolling, and completing the study intervention in 12 patients. **Secondary Objectives:** To assess the safety and tolerability of ketamine-assisted therapy in the study population. To determine the prevalence of existential distress in patients with non-operable GI cancers.
Endpoints:	**Primary Endpoint:** The recruitment, consent, enrollment, and study completion of 12 patients. Study completion defined as participating in at least 2/3 of the 3 KAP sessions. **Secondary Endpoints:** The frequency of adverse events (AEs) and serious adverse events (SAEs) characterized by type, severity (as defined by the NIH CTCAE, version 5.0), seriousness, duration, and relationship to study treatment. The proportion of screened patients that meet criteria on the Existential Distress Scale (EDS: Single domain ≥ 3 or total score ≥ 6)
Study Population:	**Key Inclusion Criteria:** • Subjects with non-operable GI cancers who requiring multi-modal treatment (e.g. surgery +/- chemo +/-radiation) and have a a high likelihood of recurrence and/or treatment failure in the opinion of the treating investigator

	• Screen positivity for existential distress on the EDS, defined as scoring ≥ 3 on any of the 10 component domains, or a total score ≥ 6 • ECOG Performance Status ≤ 2.
	Key Exclusion Criteria: • Personal history or first- or second-degree relatives with schizophrenia, bipolar affective disorder, delusional disorder, schizoaffective disorder, psychosis, or other psychotic spectrum illness. • Currently meeting DSM-5 criteria for Dissociative Disorder, or other psychiatric conditions judged to be incompatible with the establishment of rapport or safe exposure to ketamine. • Currently meeting DSM-5 criteria for Cluster B Personality Disorder. • Severe depression requiring immediate standard-of-care treatment (e.g., hospitalization). • Suicidal ideation over the past month as assessed as a yes to question 3, 4, or 5 on the Columbia-Suicide Severity Rating Scale, Suicidal Ideation section • Cancer with known CNS involvement, previously treated brain metastasis, or other major CNS disease. Current or history within the last two years of meeting DSM-V criteria of substance use disorder (excluding caffeine and nicotine). Current substance use disorders may be identified through the drug urine screening test. • Congestive heart failure, including all New York Heart Association Classes. • Angina pectoris, cardiac hypertrophy, cardiac ischemia, myocardial infarction • Uncontrolled hypertension at the time of enrollment (BP>140 systolic or 90 diastolic), coronary artery disease, artificial heart valve • Prolonged or congenital long QT syndrome (>450 ms), serious cardiac arrhythmias, tachycardia, a clinically significant screening ECG abnormality • History of hypersensitivity to ketamine • Receiving ketamine treatments for psychiatric condition within the past 6 months • Seizure disorder • Moderate to severe dementia • History of significant traumatic brain injury • Requires the use of supplemental oxygen.

	• Any other condition that would, in the Investigator's judgment, contraindicate the subject's participation in the clinical study due to safety concerns or compliance with clinical study procedures (e.g., infection/inflammation, intestinal obstruction, unable to swallow medication, [patients may not receive the drug through a feeding tube], social/ psychological issues, etc.) • Subjects taking prohibited medications. A washout period of prohibited medications for a period of at least five half-lives should occur prior to study registration. These medications include antipsychotic medications, doses of benzodiazepines in excess of 20mg diazepam equivalents per day.
Study Intervention:	Ketamine, 0.5-1.2mg/kg, IM
Study Duration:	1 year
Participant Duration:	6 months

1.2 Schema


12 eligible patients with existential distress associated with non-operable cancers
Baseline preparatory session
Ketamine Sessions (2-7 days apart)
1
2
3
Integration session
Follow-up

1.4 Schedule of Events

Activity	**Screening**	**Preparatory Session (Baseline)**	**Ketamine Sessions[1]**			**Integration Session**	**Follow-Up[2]**		
Visit			1	2	3		14 Days	30 Days	90 Days
(Window in days)	-60	0				0	(±3)	(±7)	(±7)
Informed Consent	X								
Demographics	X								
Medical History	X								
Eligibility Criteria	X								
Registration[3]	X								
Clinical and Laboratory Assessments[4]									
Vital Signs[5]	X		X[6]	X[4]	X[4]				
Physical Exam	X								
ECOG Score	X								
ECG	X		ACI						
Adverse event collection[7]	X	X	X	X	X	X	X		
Concomitant medications	X	X	X	X	X	X	X		
Complete Metabolic Panel	X								
Urine Drug Screen	X								
Pregnancy Test[8]	X								
Study Intervention									
Evaluation and Screening[9]			X	X	X				

Activity	Screening	Preparatory Session (Baseline)	Ketamine Sessions[1]			Integration Session	Follow-Up[2]		
Visit			1	2	3		14 Days	30 Days	90 Days
(Window in days)	-60	0				0	(±3)	(±7)	(±7)
Ketamine Administration[10]			X	X	X				
Psychotherapy		X	X	X	X	X			
Assessments									
EDS[11]	X	X	X	X	X		X	X	X
QIDS-SR-16[12]		X	X	X	X		X	X	X
C-SSRS Baseline/Screening[13]	X								
C-SSRS Since Last Visit[14]		X	X	X	X	X	X		
MEQ-30[15]			X	X	X				
NADA[16]			X	X	X				
DADDS[17]		X	X	X	X		X	X	X
FACIT-Sp[18]		X					X	X	X
Storyline Integrative Assessment[19]		X					X	X	X

[1] Ketamine will be given during three sessions, 2 to 7 days apart. Questionnaires, with the exception of the MEQ, may be completed up to 1 day prior to the ketamine session.
[2] Follow-up will be based on time since completion of the integration session.

3 To register eligible patients on study, complete a Clinical Trials Office Subject Registration Form and submit to CTORegistrations@hci.utah.edu.
[4] Laboratory assessments should be completed within 28 days of enrollment.

[5] Vital signs include systolic/diastolic blood pressure, heart rate, respiration rate, pulse oximetry andweight.

[6] Cardiovascular measures during KAP session (blood pressure, O2 sat, heart rate) will be completed within ten minutes prior to session and at 40 min and 2 hours post-administration. Vitals will be reviewed by an on-site MD with ACLS certification. A crash cart and code response team will be available.
[7] Adverse events and conmeds will be recorded at the time of the session. Subjects may also be contacted by study staff after the session to assess for any additional adverse events or conmed changes.

8 Pregnancy test (serum or urine) must be obtained at screening and ≤ 8 days prior to ketamine administration for all women of childbearing potential and as clinically indicated while on trial.
[9] Evaluation and screening to include the items listed in Section 6.1.2.
[10] Ketamine will be administered according to Section 6.1.3.

[11] Existential Distress Scale (EDS). See Appendix 2.

[12] Quick Inventory of Depressive Symptomatology (QIDS-SR-16). See Appendix 3.

[13] Columbia-Suicide Severity Rating Scale Baseline/Screening (C-SSRS). See Appendix 4.

[14] Columbia-Suicide Severity Rating Scale since Last Visit (C-SSRS). To be completed at any time during study participation if a subject is rated as of moderate or high risk on the Baseline/Screening C-SSRS. See Appendix 5.

15 Mystical Experiences Questionnaire (MEQ-30) should be completed after ketamine administration. See Appendix 8.
[16] Nondual Awareness Dimensional Assessment. See Appendix 7.
[17] Death and Dying Distress Scale. See Appendix 9.
[18] The Functional Assessment of Chronic Illness Therapy. See Appendix 6.
[19] See Section 3.3.

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

To assess the feasibility of recruiting, consenting, enrolling, and completing the study intervention for 12 patients.

Primary endpoint: The recruitment, consent, enrollment, and study completion of 12 patients. Study completion defined as participating in at least 2/3 of the 3 KAP sessions.

2.2 Secondary Objectives

2.2.1 To assess the safety and tolerability of ketamine-assisted therapy in the study population.

Secondary Endpoint: The frequency of adverse events (AEs) and serious adverse events (SAEs) characterized by type, severity (as defined by the NIH CTCAE, version 5.0), seriousness, duration, and relationship to study treatment.

2.2.2 To determine the prevalence of existential distress in patients with non-operable GI cancers.

Secondary Endpoint: The proportion of screened patients that meet criteria on the Existential Distress Scale (EDS: Single domain ≥ 3 or total score ≥ 6).

2.3 Exploratory Objectives

2.3.1 To assess the effect that KAP has on symptoms of existential distress and depression in patients with non-operable GI cancers as measured by the EDS and QIDS-SR-16.

Exploratory Endpoint: Mean change in score on EDS and QIDS-SR-16 from baseline to 2 weeks post completion of intervention.

2.3.2 To assess the effect that qualitative experiential aspects of the ketamine experience have on subsequent change to depression and existential distress measures using the Mystical Experiences Questionnaire (MEQ-30) and Nondual Awareness Dimensional Assessment (NADA)

Exploratory Endpoint: Correlation between total score on the MEQ-30 and NADA and change in the EDS score at the 2 week primary outcome time point.

2.3.3 To assess the effect that KAP has on symptoms of existential distress and depression in patients with non-operable GI cancers as measured by the Spiritual Well-Being (FACIT-Sp)

Exploratory Endpoint: Mean change in score on FACIT-Sp from baseline to Day 30 post completion of intervention.

2.3.4 To develop an algorithm with Storyline Health technology to rapidly discover the most predictive and information rich components in the assessment of existential distress and its treatment response.

Exploratory Endpoint: Identification of a behavioral phenotype that better predicts a response to ketamine intervention.

2.3.5 To evaluate the completion rate of questionnaires using the Storyline platform.

Exploratory Endpoint: The percentage of questionnaires completed.

3 BACKGROUND AND RATIONALE

Symptoms of existential distress in patients with life-threatening cancer diagnoses are common, difficult to meaningfully treat, and cause extensive suffering at the end of life.[1] Rates of existential distress in this population in general are estimated to be as high as 25% to 50%[2]. Existential distress, along with associated symptoms of anxiety and depression, have been shown to predict poor longitudinal outcomes, reduced quality of life (QoL), higher utilization of opioid analgesics, and care-provider burnout.[3-5] There is evidence to suggest that existential distress- as measured by validated tools- is a distinguishable phenomenon from other current recognized DSM diagnoses such as depressive and anxiety disorders.[6,7]

In patients with cancers of the GI tract, surgery is essential for curative intent. In patients for whom curative surgical resection is not an option, whether due to distant metastatic spread, local tumor invasion or patient comorbidities, the absence of curative options further contributes to the development of existential distress, potentially leading to decreased QoL, higher pain scores and even shorter survival. In patients with advanced non-small-cell lung cancer, several previous reports have suggested that early palliative intervention may increase overall survival[8-11] and/or QoL. This may be partially mediated by resources that address aspects of existential distress.

Current treatments for existential distress in this population are limited. Usually, sedative medications are utilized initially to control symptoms, primarily GABA agonist medications. In severe cases patients are rendered minimally conscious utilizing intravenous infusions of medications such as propofol or phenobarbital. This is referred to as *terminal sedation (Rousseau, 2001)*. These interventions serve to lessen individual distress, but come at a cost of diminished awareness and limited meaningful interaction with family and friends at end of life.

A variety of types of therapy are utilized in addition to medications, most of which seek to normalize and validate the symptoms, whether as an individual or group. Multiple other options, such as dignity therapy, seek to help elucidate the legacy that will be left after the patient's death (Vuksanovic et al., 2017). These therapies have been shown to be effective (Cuevas et al., 2021) but the availability of experienced practitioners, short duration of effect and duration of therapy (8 weeks) limits the utility in those with severe symptoms or limited life expectancy. Given advances in medical therapies, the number of people living with terminal illnesses is increasing (Etkind et al., 2017). Additional therapies will be necessary to deal with the increasing burden of mental health issues that will invariably accompany this rise.

3.1 Ketamine

Ketamine, one of the most used anesthetic medications in the world and one of the World Health Organization's essential medications, is a dissociative anesthetic that exerts pharmacological actions through antagonism at the NMDA receptor, altering glutamatergic tone in the brain (Zorumski et al., 2016). Intranasal ketamine in the form of Spravato, or the s-enantiomer of racemic ketamine, recently received FDA approval for the treatment of depression, and multiple trials have shown the effectiveness of intravenous ketamine infusions for acute depression and suicidality (Abbar et al., 2022; Andrade, 2017; Ekstrand et al., 2022; Fava et al., 2020; Mandal et al., 2019; Singh et al., 2016).

There is evidence that ketamine infusions can have a beneficial effect on mental health disorders without associated psychotherapy, including for the treatment of major depressive disorder. Ketamine-assisted psychotherapy (KAP) delivers this treatment in the context of a psychotherapeutic process and seems to increase the positive benefits of this intervention, by modulating the self-awareness and self-referential processing of the participant and potentially prolonging therapeutic effect (Bottemanne et al., 2022; Dore et al., 2019; Krupitsky & Grinenko, 1997; Mathai et al., 2022). There is a strong reason to believe that this aberrant self-referential processing plays a part in existential distress. Currently there is limited literature regarding the use of ketamine and existential distress, but initial case reports point to the need for larger more focused studies to ascertain benefits. In a case series and an in an open label-trial, oral ketamine was found to be a rapid, safe, and tolerable treatment for depression in patients receiving hospice care (S. A. Irwin & Iglewicz, 2010; Stefanczyk-Sapieha et al., 2008). Ketamine's anti-nociceptive properties also suggest it may be an effective treatment for patients often dealing with intractable pain symptoms (Castellanos et al., 2020)

Ketamine has a favorable pharmacological profile as it relates to drug interactions, side effects, and time to therapeutic response. It is used in the adult and pediatric population as an anesthetic and analgesic in surgery, acute care, and trauma and pain management. It has been used in management of chronic pain in hospice and palliative care populations for breakthrough and chronic pain. IM Ketamine has a 90-95% bioavailability, has a short half-life, and it does not depress the respiratory drive. Many of those suffering from existential distress are currently taking at least one SSRI, SNRI or MAOI anti-depressant, which may take 4-6 weeks to full therapeutic response and relief of symptoms, time which a population of patients with limited life expectancy lacks. Ketamine's antidepressant effects can be observed and measured within hours to days of administration.

This study will contribute to the knowledge base around the use ketamine as a medicine used in alleviating emotional suffering at the end of life. There are currently limited tools for this condition. This study will inform a larger randomized controlled trial.

3.2 Patient Population Background

Patients with advanced cancers of the GI tract often have limited treatment options and poor prognosis. These cancers can originate from a wide variety of sources and include hepatic, biliary, pancreatic, small bowel, colon and rectal cancers.

Treatment modalities such as chemotherapy, immunotherapy or surgical resection often carry significant morbidity. Patients for whom curative surgical resection is not an option, whether due to distant metastatic spread, local tumor invasion or patient co-morbidities, may have significant physical symptoms as well as concomitant existential distress.

Existential distress is distress that originates from complexities and contradictions within one's lived experience and relationship to the world around them. It occurs when meaning and value become "unclear" (Lo 2018). Existential distress appears to be a distinguishable phenomenon from other current recognized DSM diagnoses such as depressive and anxiety disorders.[6,7]

Symptoms of existential distress in patients with life-threatening cancer diagnoses are common, difficult to meaningfully treat, and cause extensive suffering at the end of life.[1] Rates of existential distress patients with advanced cancer are estimated to be as high as 25% to 50% (Grassi 2017).

Existential distress, along with associated symptoms of anxiety and depression, have been shown to predict poor longitudinal outcomes, reduced quality of life, higher utilization of opioid analgesics, and care-provider burnout.[3-5]

3.3 Storyline Health Assessments

3.3.1 Overview

Storyline is a flexible research platform that will be used to deliver assessments during the course of the study. Storyline extracts features from video, audio, and natural language and overlays it with other data sources like patient records, genome data and outcomes.

Participants are owners of their data and can access it at any time, and even delete it. However, the study will not be able to provide direct meaningful interpretations for participants. Note, that participants may be able to choose some non-research interactions within the Storyline app, such as what celebrities they look like. This is not considered a benefit nor will be included in the research data, it's for entertainment purposes for the participants.

3.3.2 Storyline Core Questions of Health

The baseline assessment is designed to mimic a typical clinical psychiatric diagnostic interview and a neurological assessment. The psychiatric portion is a 60- minute program broken into six different 10-minute assessment sessions. The neurological portion is a 10-mintute assessment.

Patients will be notified through the Storyline app on their smartphone or smart device to complete the various study assessments. Storyline manages reminders and makes the process simple.

The objective is to create an effective and fast algorithm for feature selection and question selection to build assessments, diagnostic biobehavioral markers and predictive models from Storyline captured speech, vocal and facial data. The proposed algorithm has 3 components, including (1) rapid feature and question filtering based on variance, (2) feature selection using a method that integrates mutual information and random forest importance scores and (3) question selection using a deep learning method that ranks the predictive value of each question using the optimized features. The steps are as follows:

Rapid Question Filtering – The first step in the Short Story algorithm will be to filter questions, assessments and A.I. features in the storyARC and storyTIME files that have little information content. To do this, we will compute the variance for each measured feature for each question in the data for all people in a customer's pilot study. The variance is scaled to account for differences in units. We then sum the variance for each feature for each question, apply a min-max absolute scale for interpretation that scores questions from 0 (low information content) to 100 (high information content). The results will enable users to rapidly screen, rank and prune questions with little to no information content by pruning the bottom 25% of tested candidate questions.

Feature Selection: Storyline AI measures over 20,000 speech, vocal and facial features from the responses for each question and many are correlated or not useful for detecting some phenotypes of interest. Therefore, in this second step, Short Story technology performs a feature selection analysis that uncovers the most useful features for each tested question in an assessment for predicting a particular phenotype or outcome. The major objective is to uncover the best questions and features when the available data has limited sample size and classes are imbalanced. Our approach will involve implementing the qualitative mutual information (QMI) feature selection algorithm previously detailed by others and proven for high dimensional data, including microarray data for tens of thousands of genes (Nagpal and Singh, 2019). The algorithm will provide a score that combines random forest (RF) feature importance scores with mutual information to obtain a QMI value for each feature. QMI is more powerful than random forest (RF) importance or mutual information alone for feature selection, as previously described (Nagpal and Singh, 2018). In brief, RF will be applied to the speech, vocal and facial feature sets separately for each question and the importance scores of each feature will be calculated, as well as mutual information. RF importance scores will be converted to Preference scores and multiplied by the mutual information to define QMI values for each feature. The features will then be ranked by QMI values and features with a QMI > 0 will be retained. The results will return the most useful speech, facial and vocal features for each question. The usefulness of the features is determined from their ability to differentiate the two classes in a study, such as control versus sick patients.

This approach has many advantages, including broad utility with few parameters to tune, applications to diverse data types with few samples and acceptable computational speed. RF importance scores are powerful for ranking correlated features. Mutual information, which determines the amount of information one random variable can provide about another variable, is then incorporated to further help remove irrelevant and redundant features. When accounting for accuracy and computational efficiency, this combined approach outperforms most methods, including filter, wrapper, embedded and hybrid feature selection strategies (Nagpal and Singh, 2019).

Question Selection: The final step of the Short Story algorithm will provide a score that determines the individual questions that should be retained in a new assessment and those that can be eliminated. In this approach, the input is all of the candidate questions and their optimized speech, vocal and facial features revealed from Short Story Score #2. The individual questions and question combinations that show the most value for predicting the classes of interest will then be determined. We will create a simple two-layer neural network that is architected to take Storyline speech, vocal and facial features as inputs to predict the

phenotypic classes of interest. The algorithm will be designed such that questions are tested in all possible pairwise combinations with 5-fold cross validation. The mean accuracy for predicting the target phenotype is determined for each question combination. Each pairwise question combination is then assigned an index. To compute the Short Story score for each question, we multiply the index and the mean classification accuracy for all question pairings in which that question was included in the predictive model. This vector of index*accuracy values is summed to yield a score and then the scores for all of the candidate questions are min-max scaled to create the final Short Story question ranking score from 0-to-100, where a high score indicates important questions, and a low score indicates questions that can be pruned. The final results will return the ranking for each question and the mean classification accuracy values for each question.

3.3.3 Psychiatric and Psychology Assessment Components:

This part of the assessment is a 60-minute program broken into six 10-minute assessments of (i) physical symptoms, (ii) mood & emotion, (iii) cognition, (iv) homeostasis (ie. eating, sleeping, activity patterns) (v) social support and (vi) psychological associations. The program was created, in part, with our collaborator, Dr. Brian Mickey MD PhD (clinical psychiatrist) from a proven set of psychiatric interview questions and methods for DSM-5 diagnoses of depression, bipolar, anxiety, psychosis, neurocognitive disorders (dementia and delirium), suicidality, addiction, trauma and physical health. This interview uses open-ended questions that evaluate RDoC domains and create a caring and natural interview experience that is non-threatening using “normalization”, “reduction of guilt” and “symptom exaggeration” techniques, as well as providing safety, transparency, education and logical flow. Cognition is assessed, in part, using established clinical tests of cognitive functioning, including tests of (i) orientation (date, day of the week, location), (ii) short-term memory, (iii) long-term memory and recall, (iv) semantic fluency, (v) verbal fluency, (vi) working memory, (vii) attention and (viii) self-initiation. In addition, open-ended questions are included that ask for descriptions of (1) concerns about brain functioning, memory, concentration and fatigue, (2) any noticeable changes in memory or thinking, brain fog, headaches, (3) social interactions and perceived support, and (5) a 1-5-minute story about “something that happened to you this week”. The psychological associations assessment uses open-ended descriptions (“What does this make you think of?”) to capture responses to neutral, positive and negative cues, including Eckman faces (neutral, happy, sad, angry, disgust, surprise, contempt), Open Affective Standardized Image Sets (OASIS) and Affective Norms for English Words (ANEW) with valence, arousal or dominance characteristics predictive of mental illness (ie. death, cruelty, trouble, carefree, good, and praise). Finally, the Storyline assessment includes the standard PHQ-2, GAD-2 and PCL-2 questionnaires of clinical depression, anxiety and trauma symptoms as internal controls for clinical symptomology.

The neurological assessment developed by Storyline is 10 minutes long and is similar to a standard of care neurological exam. It includes questions that test eye movement, facial expression, speech, finger movements, hand movements, cognition and drawing. The material for this assessment is derived from the following leading clinical neurology textbook: "Neurological Examination Made Easy 6th Edition” by Geraint Fuller MD FRCP.

3.3.4 Deep Cognitive and Behavioral Assessments During Treatment

Participants will be asked to perform a 10-minute “Well-being” assessment that includes open-ended questions about major domains of health. Examples include how they are, concerns, physical symptoms, emotional symptoms, social interactions and perceived support, medications and missed pills, energy and activity, sleep, a 1-5-minute story describing something that happened to them during the week and tests of short-term memory, working memory and attention.

4 STUDY DESIGN

This study is an open-label feasibility study that will enroll a total of 12 patients with non-operable GI cancers suffering with existential distress. The study intervention for KAP will include a preparatory session, a total of three 2.5-3 hour therapy sessions which will occur 2-7 days apart, an integration session, and follow-up visits at 14, 30, and 90 days. Ketamine will be administered at a starting does of 0.5 mg/kg and can be titrated up to 1.2 mg/kg based on patient response. The sessions will utilize eye-shades and a music track played over headphones. This will involve a therapist trained in KAP present 1:1 for all sessions with a physician available on site for medical evaluation, medication administration, support and backup.

We hypothesize that this study design will be feasible and ketamine can be administered safely. This study will better characterize the category of ‘existential distress’ which is variably described in the literature, separable as a phenomenon from DSM 5 mood and anxiety disorders, and a set of symptoms that cause significant distress for patients and care givers. To better characterize and understand symptoms and predictors of existential distress we will administer an existential distress screening instrument (the Existential Distress Scale) along with a broad psychosocial assessment to screen for patient enrollment as well as examine psychosocial predictors. We will then utilize the Storyline Health platform through the study process to build and refine a set of behavioral biomarkers to characterize existential distress.

4.1 Study Duration

Study duration will be approximately 1 year.

4.2 End of Study

A subject is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Events.

The study will end when the last subject completes the last visit or last contact, discontinues from the study, or is lost to follow-up, whichever occurs first. In addition, the sponsor may terminate the study at any time. If at any time, the sponsor terminates the study any subjects receiving clinical benefit from the study intervention may roll over to an expanded access protocol, if available, to ensure continued access to the study medication.

5 STUDY POPULATION

Potential study participants must meet all inclusion criteria and no exclusion criteria to be deemed eligible for trial participation. To ensure subject safety, all subjects must be deemed eligible at the time of study registration and must continue to meet eligibility criteria up to ketamine dosing. This eligibility checklist is used to determine subject eligibility and will be filed with the enrolling investigator's signature in the subject research chart.

5.1 Inclusion Criteria

1. _____ Subject aged ≥ 18 years.
2. _____ Subjects with non-operable GI cancers requiring multi-modal treatment (e.g. surgery +/- chemo +/-radiation) and have a a high likelihood of recurrence and/or treatment failure in the opinion of the treating investigator.
3. _____ Screen positivity for existential distress on the EDS, defined as scoring ≥ 3 on any of the 10 component domains, or a total score ≥ 6
4. _____ ECOG Performance Status ≤ 2.
5. _____ Adequate hepatic function as defined as:
    - Total Bilirubin ≤ 1.5x institutional upper limit of normal (ULN) unless elevated bilirubin is related to Gilbert's Syndrome
    - AST(SGOT)/ALT(SGPT) ≤ 3 × institutional ULN
        - Subjects with liver metastases will be allowed to enroll with AST and ALT levels ≤ 5 x ULN.
6. _____ For subjects of childbearing potential: Negative pregnancy test or evidence of post-menopausal status. The post-menopausal status will be defined as having been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
    - Subjects < 50 years of age:
        - Amenorrheic for ≥ 12 months following cessation of exogenous hormonal treatments; and
        - Luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution; or
        - Underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
    - Subjects ≥ 50 years of age:
        - Amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments; or
        - Had radiation-induced menopause with last menses >1 year ago; or

- Had chemotherapy-induced menopause with last menses >1 year ago; or
- Underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

7. _____ Subjects of childbearing potential and subjects with a sexual partner of childbearing potential must agree to use a highly effective method of contraception as described in Section 5.3.1.
8. _____ Subjects with a sexual partner of childbearing potential must agree to use a condom during intercourse for 24 hours post- ketamine dose.
9. _____ Agree to refrain from using any psychoactive drugs, including alcoholic beverages, ondansetron, cannabis, and non-routine PRN medications within 24 hours of each ketamine administration. Exceptions include daily use of caffeine, nicotine, and opioid pain medication (see Section 6.5.1).
10. _____ Able to provide informed consent and willing to sign an approved consent form that conforms to federal and institutional guidelines.
11. _____ Agree that for one week preceding the ketamine session, he/she will refrain from taking any nonprescription medication, nutritional supplement, or herbal supplement except when approved by the research team. Exceptions will be evaluated by the research team and will include acetaminophen, non-steroidal anti-inflammatory drugs, and common doses of vitamins and minerals.
12. _____ Agree not to use nicotine for at least 2 hours before the ketamine administration or for the duration of the ketamine session.
13. _____ Agree to consume approximately the same amount of caffeine-containing beverage (e.g., coffee, tea) that he/she consumes on a usual morning, before arriving at the research unit on the morning of the ketamine session. If the subject does not routinely consume caffeinated beverages, he or she must agree not to do so on the day of ketamine administration.
14. _____ Subjects requiring opioid use for pain are on a stable pain management regimen or do not experience clinically significant sedation during opioid use.
    - Note: Long-acting opioid medications (e.g., oxycodone sustained-release, morphine sustained release) will be allowed if the last dose occurred at least 6 hours before ketamine administration; such medication will not be taken again until at least 6 hours after ketamine administration.
15. _____ Fluent in English.
16. _____Reading literacy and comprehension sufficient for understanding the consent form and study questionnaires, as evaluated by study staff obtaining consent.
17. _____ Have a support person who is be able to escort the subject home from the ketamine dosing sessions.
    - Note: The use of ride services will not be permitted (e.g., Uber, Lift, taxi, etc.)

5.2 Exclusion Criteria

1. _____ Received ketamine treatments for a psychiatric condition within 6 months of enrollment.
2. _____ Personal history or first- or second-degree relatives with schizophrenia, bipolar affective disorder, delusional disorder, schizoaffective disorder, psychosis, or other psychotic spectrum illness.
3. _____ Currently meeting DSM-5 criteria for Dissociative Disorder, or other psychiatric conditions judged to be incompatible with the establishment of rapport or safe exposure to ketamine.
4. _____Currently meeting DSM-5 criteria for Cluster B Personality Disorder.
5. _____ Severe depression requiring immediate standard-of-care treatment (e.g., hospitalization).
6. _____ Suicidal ideation over the past month as assessed as a yes to question 3, 4, or 5 on the Columbia-Suicide Severity Rating Scale, Suicidal Ideation section
7. _____ Cancer with known CNS involvement, previously treated brain metastasis, or other major CNS disease.
8. _____ Current or history within the last two years of meeting DSM-V criteria of substance use disorder (excluding caffeine and nicotine). Current substance use disorders may be identified through the drug urine screening test.
9. _____ Current evidence of uncontrolled, significant intercurrent illness including, but not limited to, the following conditions:
    - Cardiovascular disorders:
        - Any grade congestive heart failure, unstable angina pectoris, serious cardiac arrhythmias including tachycardia, or clinically significant screening ECG abnormalities.
        - Cardiac hypertrophy or artificial heart valve.
        - Stroke (including transient ischemic attack [TIA]), myocardial infarction (MI), or other ischemic events, or thromboembolic event (eg, deep venous thrombosis, pulmonary embolism), and/or significant coronary artery disease within 3 months before the first dose.
        - QTc prolongation defined as a QTcF > 450 ms.
        - Known congenital long QT.
        - Uncontrolled hypertension defined as ≥ 140/90 as assessed from the mean of three consecutive blood pressure measurements taken over 10 minutes.

- Seizure disorder
- Moderate to severe dementia
- History of significant traumatic brain injury
- Requires the use of supplemental oxygen.
- Renal insufficiency as defined as creatinine clearance < 40 mL/min calculated by Cockcroft-Gault formula
- Any other condition that would, in the Investigator's judgment, contraindicate the subject's participation in the clinical study due to safety concerns or compliance with clinical study procedures (e.g., infection/inflammation, intestinal obstruction, unable to swallow medication, [subjects may not receive the drug through a feeding tube], social/ psychological issues, etc.)

10. _____ Known HIV infection with a detectable viral load within 6 months of the anticipated start of treatment.

    Note: Subjects on effective antiretroviral therapy with an undetectable viral load within 6 months of the anticipated start of treatment are eligible for this trial.

11. _____ Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination, radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), or hepatitis C.

    Note: Subjects with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Subjects positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

12. _____ Medical, psychiatric, cognitive, or other conditions that may compromise the subject's ability to understand the subject information, give informed consent, comply with the study protocol or complete the study.

13. _____ Known prior severe hypersensitivity to ketamine or any component in its formulations (NCI CTCAE v5.0 Grade ≥ 3).

14. _____ Subjects taking prohibited medications as described in Section 6.5.1. A washout period of prohibited medications for a period of at least five half-lives or as clinically indicated should occur before the start of treatment.

I certify that this patient meets all inclusion and exclusion criteria for enrollment onto this study.

Investigator Signature	**Date**	**Time**

5.3 Registration

Subjects must complete all screening procedures and meet all of the eligibility requirements before registration. Study-related screening procedures can only begin once the subject has signed the consent form. Subjects must not begin protocol treatment prior to registration.

Treatment should start as soon as logistically possible after registration.

To register eligible subjects on study, complete a Clinical Trials Office Subject Registration Form and submit to CTORegistrations@hci.utah.edu.

For sites outside of Huntsman Cancer Institute, submit registration forms to MultisiteRegistrations@hci.utah.edu

5.3.1 Contraception

Non-clinical and clinical data describing the effects ketamine on lactation, sperm, and teratogenicity are limited. Therefore, subjects of childbearing potential should have a negative pregnancy test at the time of screening and use a highly effective form of contraception for the duration of study treatment and for at least 14 days after ketamine administration.

Subjects should be instructed to use a condom for 24 hours after the ketamine dose.

Acceptable highly effective contraceptive methods include:

- Bilateral tubal occlusion
- Vasectomized partner
- Intra-uterine devise (IUD) or hormone-releasing system (IUS)
- Any hormonal (estrogen combined with progesterone or progesterone alone) contraception associated with inhibition of ovulation: implanted, oral, intravaginal, transdermal, or injectable.
- Spermicide with a compatible barrier method (i.e. diaphragm, sponge, or male or female condoms).
- Abstinence from heterosexual intercourse.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but do not meet subject eligibility criteria. These subjects will not be entered into the study or begin study intervention. However, minimal information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements. Minimal information includes, but may not be limited to, demography, screen failure details, eligibility criteria, and any serious adverse event (SAE) experienced during screening, but prior to being deemed ineligible. Adverse events and SAEs will not be collected after a subject is deemed ineligible. Any AEs/SAEs related to a screening procedure will be followed until resolution.

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened at the Investigator's discretion.

5.5 Strategies for Recruitment

Potential patients will be identified by Investigators in the setting of their outpatient clinics. Social work team members on each oncology service will help identify potential patients during routine clinic encounters.

5.5.1 Number of Subjects

The study will enroll 12 subjects.

5.5.2 Number of Study Sites

This will be a single-center trial run at the Huntsman Cancer Institute at the University of Utah.

6 STUDY INTERVENTION

6.1 Ketamine Assisted Psychotherapy

Ketamine-assisted psychotherapy will be administered standard of care by the therapist team in the HMHI Park City Ketamine-Assisted Psychotherapy Clinic. This team has been trained specifically in this modality of treatment by the Psychedelic Research and Training Institute (PRATI). This modality of therapy involves an initial experiential phase following ketamine administration of approximately 1 hour that is supportive and non-directive in nature and may utilize eye-shades and music playlists via headphones. Interventions during this phase of the session are minimal, supportive, and largely directed towards helping the patient move through any difficult emotions or experiences arising. The next phase of the 3 hour session involves more directed psychotherapeutic engagement where participants begin to explore and discuss content that arose during their experience, how this content may be related to underlying issues that bring them into this study (existential distress, grief, depressive symptoms, anxiety), and strategies to integrate this material or insights gained into their everyday lives. Modalities employed by our therapist team largely center around Acceptance and Commitment Therapy (ACT) techniques however also include – as clinically indicated- other modalities such as CBT, psychodynamic approaches, and Internal Family Systems (IFS), and Internal Family Systems (IFS).

6.2 Ketamine Administration Schedule

Ketamine and all other supportive medications described in this guideline will be stored in accordance with State and Federal regulations. Medication retrieval, documentation, and wasting will follow applicable organizational policies and guidelines related to automated dispensing cabinets, controlled substances, and the storage, labeling, and discarding of drugs. Each vial of ketamine will be used to provide the desired dose for a single patient, and the remainder of the vial will be promptly wasted.

6.2.1 Personnel required for administration of ketamine:

- Medical doctor will be in the same room as the patient or onsite and immediately available throughout ketamine administration and the monitoring period

- Vital signs will be performed by either a medical assistant, clinic therapist, nurse, or medical doctor. All vital signs will be reviewed by an MD during the session at the time they are taken.

6.2.2 Screening prior to ketamine-assisted psychotherapy:

- Evaluation and screening **prior to first visit**
  - Psychiatric evaluation and review of medical history
  - Physical exam
- Evaluation and screening **immediately prior to each administration**
  - Confirm allergy list
  - Confirm patient has been NPO (except for water) for at least 4 hours prior to treatment
  - Medication history
    - Confirm no use of sedatives or psychostimulants for 12 hours prior to treatment
    - Confirm no use of MAO inhibitors for 2 weeks prior to treatment
  - Brief physical assessment
    - Blood pressure
      - If blood pressure > 140/90 mmHg, then make a clinical decision regarding risks/benefits of administration of ketamine
      - If blood pressure > 160/100 then hold ketamine and re-check after five minutes. May repeat this process twice.
      - If blood pressure remains over 160/100 then ketamine will not be given.
    - Other parameters that must be met for ketamine administration
      - Oxygen saturation > 92% on room air
      - Respirations > 8 breaths per minute
      - Patient must be fully awake
      - Patient must be able to move all extremities
  - Verify the patient has a responsible adult to escort them home
    - Patients may take any mode of transportation as long as they are accompanied by an escort
    - Ketamine will not be administered if an escort cannot be identified

6.2.3 Administration of ketamine

- To be administered by a medical doctor or nurse
  - Double check of dose/volume to be administered to the patient
- Intramuscular administration
  - Doses can range 0.5-1.2 mg/kg. Starting dose for all participants will be 0.5mg/kg.
  - Dose can be titrated up to maximum of 1.2 mg/kg or titrated down to 0.5 mg/kg based on response and clinical judgement.
  - Dose will be administered by injecting into large muscle mass (eg, deltoid, gluteal muscle, thigh)

6.2.4 Monitoring after administration

- During KAP session
  - Check blood pressure 40 minutes and 2 hours after ketamine administration
    - Give clonidine 0.1 mg po in clinic if blood pressure is greater than 180/110. If blood pressure remains elevated 1 hour after clonidine administration, transfer patient to a higher level of care.
    - Initiate emergency response procedures if blood pressure is greater than 180/110 and the patient develops symptoms of hypertensive crisis (eg, headache, vision changes)
  - Severe emotional distress or agitation as determined by MD.
    - Lorazepam 0.5 mg po/im will be available on demand. This may be repeated once after one hour for ongoing severe emotional distress or agitation.
  - Check respiratory rate at 40 minutes and 2 hours after ketamine administration
    - Initiate emergency response procedures and start continuous oxygen saturation monitoring if respiratory rate is < 8 breaths per minute or obtunded
    - Oxygen per nasal cannula available for oxygen saturation < 92%
    - Bag ventilation available
  - Nausea or vomiting
    - Ondansetron 4 mg po/im will be available on demand. This may be repeated once after one hour for ongoing nausea and vomiting.
- Following 3-hour KAP session
  - The patient must have an adult escort with them for at least 3 hours post-treatment
  - The medical doctor or medical assistant will assess for suicidal ideation or other safety concerns
  - The patient must avoid driving and operating machinery for at least 12 hours post-treatment
- Patient must meet the following objective criteria prior to leaving clinic (≥ 2 hours following ketamine administration)
  - Patient must have oxygen saturation > 92% on room air
  - Patient must have respirations > 8 breaths per minute
    - Patient must be able to take a deep breath and cough.
  - Patient must have systolic blood pressure +/- 20 mmHg of pre-administration measurement
  - Patient must be fully awake
  - Patient must be able to move all extremities

Ketamine is stored at the HMHI KAP Clinic and administered by an MD study investigator. The HMHI KAP Clinic employs a log of ketamine administration in accordance with DEA standards. Appropriate records will be kept to accurately show all dispensing activities including the return of any unused Investigational Product (IP). IP will be supplied only to subjects deemed eligible for study therapy. IP may not be dispensed to patients who have not been enrolled in the trial.

Patients will be advised to refrain from the following for 24 hours before ketamine:

- Cannabis
- Alcoholic beverages
- Psychoactive drugs
- Non-routine PRN medications
- Grapefruit, grapefruit juice, and other CYP4A inhibitors

On the day of ketamine administration, patients on opioids should not take any long-acting opioids within 6 hours prior to or 6 hours proceeding ketamine administration. Patients should consume approximately the same amount of caffeine-containing beverage (e.g., coffee, tea) that he/she consumes on a usual morning, before arriving at the research unit. If the subject does not routinely consume caffeinated beverages, he or she must agree not to do so on the day of ketamine administration. Patients should also not use nicotine for at least 2 hours before ketamine administration.

All doses of ketamine will be administered at the investigational site by qualified medical staff. The time of administration will be recorded in the patients' research charts. Any reason for deviation from the protocol-specified dose or schedule will be documented in the subject's research chart.

6.2.5 Accountability and Compliance

Ketamine is currently stored at the HMHI KAP Clinic in a secure and locked medication safe in accordance with DEA standards and is overseen by HMHI Pharmacy staff with regular inspections. This involves logging of dose, bottle # of ketamine, patient MRN, and amount of ketamine wasted per administration day with signatures of 2 clinic members present to observe the wasting of medication.

6.3 Ketamine

6.3.1 Investigational Product Supplies

Ketamine will be sourced from the current commercial supply stored at the HMHI KAP Clinic.

6.3.2 Preparation and Dispensing

The investigator or qualified personnel will prepare and dispense all investigational supplies. Appropriate records will be kept to accurately show all dispensing activates and Investigational Product (IP) will be supplied only to subjects deem eligible for study therapy. IP may not be dispensed to subjects who have not been enrolled in the trial.

The time of administration will be recorded in the patients' research charts. Any reason for deviation from the protocol-specified dose or schedule will be documented in the subject's research chart.

6.4 Adverse Event Management

Adverse events will be managed as outlined in Section 6.1.4.

6.5 Supportive Care

All supportive measures consistent with optimal patient care may be given throughout the study as deemed necessary by the treating investigator.

6.6 Concomitant Medications and Therapies

All supportive measures consistent with optimal subject care may be given throughout the study.

All administered concomitant medications (including herbal supplements) and non-medicinal therapies (including transfusions) used 28 days prior to registration, and until 30 days after the last dose of study therapy will be recorded in the subject's research chart and corresponding eCRF, if applicable.

6.6.1 Prohibited Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the active treatment period. Patients are prohibited from receiving the following therapies during the treatment phase of this trial:

- Other investigational agents
- Herbal remedies known to potentially interfere with major organ function (e.g., hypericin)
- Monoamine oxidase inhibitors
- Sedatives – any opioid, benzodiazepine, sedative hypnotic, or alcohol
- Theophylline or Aminophylline
- Sympathomimetics (excluding albuterol) and Vasopressin

Patients will be advised to refrain from the following for 12 hours before ketamine:

- Cannabis
- Psychostimulants-includes methylphenidate, any amphetamines, modafinil, or armodafinil
- Non-routine PRN medications

On the day of ketamine administration, patients on opioids should not take any long-acting opioids within 12 hours prior to or 6 hours proceeding ketamine administration. Patients should consume approximately the same amount of caffeine-containing beverage (e.g., coffee, tea) that he/she consumes on a usual morning, before arriving at the research unit. If the subject does not routinely consume caffeinated beverages, he or she must agree not to do so on the day of ketamine administration. Patients should also not use nicotine for at least 2 hours before ketamine administration. .

6.7 Duration of Therapy

Subjects will receive combined treatment until treatment discontinuation criteria is met. Upon meeting treatment discontinuation criteria, subjects will continue on the study in follow-up until study discontinuation criteria are met.

6.7.1 Criteria for the Discontinuation of Treatment

Subjects may withdraw from treatment or the study overall at any time at their request, or they may be withdrawn at the discretion of the Investigator or Sponsor for safety, behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures. In addition to the drug-specific discontinuation criteria listed in section 6, the following will result in treatment discontinuation:

- Completion of treatment study visits outlined in the Schedule of Events
- The subject or legally authorized representative requests to discontinue the study treatment and/or study procedures;
- Clinical deterioration that, in the opinion of the investigator, increases the risk to the subject;
- Adverse events or intercurrent illness that in the opinion of the investigator warrants the subject's withdrawal from study treatment;
- Significant noncompliance with the protocol schedule or treatment administration in the opinion of the investigator;
- Pregnancy

6.7.2 Criteria for the Discontinuation of Study

Subjects will be taken off study for the following:

- Completed study follow-up period;
- Participant or legally authorized representative requests to be fully withdrawn from the study;
- If, in the investigator's opinion, the continuation of the trial would be harmful to the subject's well-being;
- The subject is lost to follow-up;
- Screen failure;
- Death.

6.7.3 Withdrawal of consent

Subjects are free to withdraw from the study at any time without prejudice to further treatment. Subjects who withdraw consent for further participation in the study will not receive any further study medications or further study observation.

If a subject withdraws consent, they will be specifically asked if they are withdrawing consent to all further participation in the study including any further follow-up (e.g., survival contact telephone calls). Survival status may be obtained from public records for subjects who have withdrawn from any further follow-up contact.

6.7.4 Lost to Follow-Up

Subjects will be considered lost to follow-up only if no contact has been established by the time the study is completed, such that there is insufficient information to determine the subject's status at that time. Subjects who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing subjects throughout the study period. If contact with a missing subject is re-established, the subject should not be considered lost to follow-up and evaluations should resume according to the protocol.

When a subject is lost to follow-up, site personnel should check hospital records, the subjects' current physician, and a publicly available death registry to obtain a current survival status.

In the event that the subject has actively withdrawn consent, the survival status of the subject can be obtained by site personnel from publicly available death.

7 STUDY ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that there may be circumstances, outside of the control of the Investigator that may make it unfeasible to perform the test. In these cases, the Investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the Investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible.

7.1 General Assessments

7.1.1 Participant Consent

Before the initiation of any study procedures, all potential subjects or their legal representative must be fully informed of the risks and potential benefits of trial participation and demonstrate understanding. An informed consent document must be signed and dated by the participant or their legal representative indicating that they understand the risks and consent to participation and treatment on the study. The Principal Investigator or their appropriately trained and delegated study personnel conducting the informed consent discussion must also sign and date the document. A copy of the signed document should be provided to the subject.

Procedures, laboratory tests, or imaging performed as part of the standard of care prior to subject consent may contribute to the assessment of eligibility and/or screening procedures if performed during the screening period.

7.1.2 Medical History

The investigator or appropriately trained and delegated study personnel will collect medical history to the extent that supports the assessment of eligibility. The medical history will include any active conditions and any conditions deemed to be clinically significant by the treating investigator. The use of symptom terms should be discouraged; if possible, terms describing the principal condition or syndrome should be used.

When collecting medical history specific attention should be given to:

- History of Coronary Artery Disease
- Alcohol history (never used alcohol, current alcohol user, former alcohol user)
- Smoking history (never smoked, current smoker, former smoker)
- Pack years (average number of packs per day and number of years smoked)
- Current employment status (employed, retired, student, unknown, other)
- Insurance status (private insurance, Medicare, Medicaid, VA, military, not insured, self-pay, unknown, other)
- Substance use history; including prior history with psychedelics including ketamine.

7.1.3 Cancer History

The oncologic history of the malignancy understudy will be collected at the screening visit and will include prior regimens (duration of therapy, the best response on therapy, date of discontinuation, and reason for discontinuation), surgery, radiation therapy, and sequence.

7.1.4 Concomitant Medications

All medications currently being used by a study participant, regularly or as needed, must be reviewed and documented by the investigator or qualified designee. Specific attention should be given to medications with a protocol required washout as described in the exclusion criteria and any medication taken 28 days prior to ketamine. Refer to Section 6.5.1 for prohibited medications.

During protocol therapy, any medications taken by the patient or used to treat an adverse event will be documented in the subject's research chart and the corresponding eCRF. If a new anticancer therapy is initiated during study follow-up, the new therapy should also be recorded in the subject's research chart and corresponding eCRF. .

7.2 Safety Assessments

7.2.1 Physical Examinations and Vital Signs

Subjects will have physical examinations to include major body systems, vital signs (blood pressure, heart rate, respiration rate, and pulse oximetry), assessment of ECOG performance status (see Appendix 1). and weightat the time points described in the Schedule of Events. If necessary to facilitate scheduling, the physical exam may occur one day before study treatment.

7.2.2 Adverse Events

Adverse events experienced during trial participation will be collected per the Schedule of Events and Adverse Events Section. Each study participant will be questioned about the occurrence of adverse events in a non-leading manner.

7.2.3 Laboratory Assessments

Samples for all laboratory assessments will be drawn at the time points indicated in the Study Calendar and when clinically indicated. Laboratory tests may be performed up to 3 days before the scheduled clinic visit. All safety laboratory analyses will be performed by the local laboratory for each study center. When applicable, all safety laboratory assessments must be reviewed by the treating investigator before study drug administration. When applicable, results from the pregnancy test must also be available for review before dosing.

Table 1: Laboratory Assessments

Laboratory Assessments	
Chemistry	• Complete Metabolic Panel ○ Sodium ○ Potassium ○ Chloride ○ Carbon Dioxide ○ Alkaline Phosphatase ○ Aspartate Aminotransferase ○ Alanine Aminotransferase ○ Urea Nitrogen ○ Glucose ○ Creatinine ○ Calcium ○ Protein ○ Albumin ○ Bilirubin
Urine Drug Test	• Drug abuse panel • THC urine screen
Pregnancy	• Beta-hCG Qualitative Urine or Serum

7.2.4 12-Lead Electrocardiograms

A standard 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs. All subjects will require a single 12-lead ECG measurement according to the Schedule of Events only if clinically indicated. The parameters to be recorded are QT, QTc, PR, and QRS. All ECGs should be conducted pre-dose and Fridericia's formula will be used for all QT correction calculations.

If at any time the QTcF > 500 ms, a triplicate ECG will be performed with tracings approximately one-minute apart.

7.3 Patient Reported Outcomes

The response to study therapy will be assessed utilizing the Existential Distress Scale (EDS), Quick Inventory of Depressive Symptomatology (QIDS-SR-16), Patient Health, Columbia-Suicide Severity Rating Scale Baseline/Screening and Since Last Visit (C-SSRS), Death

Transcendence Scale (DTS), Functional Assessment of Chronic Illness Therapy - Spiritual Well-Being (FACIT-Sp), , Nondual Awareness Dimensional Assessment (NADA), Mystical Experiences Questionnaire (MEQ-30), Storyline Integrative Assessment, Patient-Reported Experience on Study Therapy, at the time points indicated in the Schedule of Events.

7.3.1 Storyline

7.3.1.1 *Psychiatric and Psychology Assessment Components:*

This part of the assessment is a 60-minute program broken into six 10-minute assessments of (i) physical symptoms, (ii) mood & emotion, (iii) cognition, (iv) homeostasis (ie. eating, sleeping, activity patterns) (v) social support and (vi) psychological associations. The program was created, in part, with our collaborator, Dr. Brian Mickey MD PhD (clinical psychiatrist) from a proven set of psychiatric interview questions and methods for DSM-5 diagnoses of depression, bipolar, anxiety, psychosis, neurocognitive disorders (dementia and delirium), suicidality, addiction, trauma and physical health. This interview uses open-ended questions that evaluate RDoC domains and create a caring and natural interview experience that is non-threatening using “normalization”, “reduction of guilt” and “symptom exaggeration” techniques, as well as providing safety, transparency, education and logical flow. Cognition is assessed, in part, using established clinical tests of cognitive functioning, including tests of (i) orientation (date, day of the week, location), (ii) short-term memory, (iii) long-term memory and recall, (iv) semantic fluency, (v) verbal fluency, (vi) working memory, (vii) attention and (viii) self-initiation. In addition, open-ended questions are included that ask for descriptions of (1) concerns about brain functioning, memory, concentration and fatigue, (2) any noticeable changes in memory or thinking, brain fog, headaches, (3) social interactions and perceived support, and (5) a 1-5-minute story about “something that happened to you this week”. The psychological associations assessment uses open-ended descriptions (“What does this make you think of?”) to capture responses to neutral, positive and negative cues, including Eckman faces (neutral, happy, sad, angry, disgust, surprise, contempt), Open Affective Standardized Image Sets (OASIS) and Affective Norms for English Words (ANEW) with valence, arousal or dominance characteristics predictive of mental illness (ie. death, cruelty, trouble, carefree, good, and praise). Finally, the Storyline assessment includes the standard PHQ-2, GAD-2 and PCL-2 questionnaires of clinical depression, anxiety and trauma symptoms as internal controls for clinical symptomology.

The neurological assessment developed by Storyline is 10 minutes long and is similar to a standard of care neurological exam. It includes questions that test eye movement, facial expression, speech, finger movements, hand movements, cognition and drawing. The material for this assessment is derived from the following leading clinical neurology textbook: "Neurological Examination Made Easy 6th Edition” by Geraint Fuller MD FRCP.

7.3.1.2 *Deep Cognitive and Behavioral Assessments During Treatment*

Participants will be asked to perform a 10-minute “Well-being” assessment that includes open-ended questions about major domains of health. Examples include how they are, concerns, physical symptoms, emotional symptoms, social interactions and perceived support, medications and missed pills, energy and activity, sleep, a 1-5-minute story describing something that happened to them during the week and tests of short-term memory, working memory and attention.

7.4 Remote Visits/Telehealth

Some study visits and/or procedures may be conducted remotely in the following circumstances:

- Telehealth visits do not present an increased risk to the participant.
- All necessary data for the trial can be collected.
- Procedures do not include research related imaging, lab samples, and/or pathology which should be conducted in person.

Note: The method of telehealth should be documented in the participants' charts.

8 ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse events

21 CRF 312.32, ICH GCP, and OHRP define an adverse event as any untoward medical occurrence whether or not considered treatment-related. This definition extends to the worsening of any preexisting condition or symptom. All adverse events experienced during trial participation should be documented in the subject's research chart and corresponding eCRF

Laboratory abnormalities should not be listed as adverse events unless deemed clinically significant by the investigator or qualified designee. An abnormal test result or findings should not be recorded as an adverse event unless the following conditions are met:

- Associated with clinical symptoms; and/or
- Requires intervention (medical, surgical, or additional diagnostic testing); and/or
- Results in a change in study drug dosing; and/or
- Deemed by the investigator or qualified designee to be an adverse event.

While disease progression should be noted in the subject's research chart, it should not be reported as an adverse event.

8.1.2 Serious Adverse Events

A serious adverse event is defined as any untoward event that is:

- Fatal;
- Life-threatening;
- Results in persistent or significant disability/incapacity;
- Medically significant;
- Causes a congenital abnormality or birth defect;
- Requires or prolongs inpatient hospitalization.

Investigator judgment must be used to assess an event as medically significant. The event may not be life-threatening or cause disability but may jeopardize the subject and require intervention to prevent the other SAE outcomes.

The following situations should not be reported as an SAE:

- Hospital admission not associated with a precipitating AE such as:
    - Treatment for a preexisting condition not associated with a new AE or the worsening of a preexisting condition;
    - Admission for social or administrative reasons;
    - Optional admission or elective surgery;
    - Observation;
    - Preplanned treatments or surgical procedures as noted at baseline;
    - Admission for the administration of blood products.

8.2 Adverse Event Reporting

The investigator and qualified designees are responsible for the detection, documentation, reporting, and follow-up of all adverse events experienced by subjects during trial participation. AEs and SAEs will be recorded from consent until 30 days after the last dose of study medication or until new cancer therapy is started. The following information will be required for each adverse event:

- Event severity as graded by the CTCAE v.5;
- The causality assessment to study medication per the below definitions;
- Expectedness
- Event duration;
- Any action taken to treat or manage the event;
- Event outcome.

8.2.1 Severity Assessment

The severity of adverse events should be assessed by CTCAE v.5. If an event is not listed in CTCAE v.5 then the assessment of severity should follow the general guidelines listed in Table 3.

Table 2: Severity assessment

Grade	Severity Description
1	Mild event that generally does not require intervention.
2	Moderate event that may require intervention.

3	Severe event that requires intervention.
4	Life-threatening event that requires urgent intervention.
5	Death.

Events meeting grade 4 or 5 severity description should be reported promptly as SAEs unless otherwise indicated in Section 8.1.2.

8.2.2 Causality Assessment

The Investigator should assess the causality or relationship of AEs and SAEs to study therapy. The Investigator should consider if there is evidence that the investigational product caused the event taking into consideration timing, organ system affected, type of event, and possible alternative etiologies. The relationship of the AE to study treatment will be reported as listed below. These categories will be defined as follows:

- Definitely related – a clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to the withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
- Probably related – a reasonable time sequence to the administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- Possibly related – a reasonable time sequence to administrations of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- Unlikely related –a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
- Not related – there is no evidence of a causal relationship between the study drug and the event and in which other drugs, chemicals or underlying disease explain the event.

Adverse events reported as definitely, probably, and possible, related to study therapy will be reported as related. In cases when the Investigator is unsure of the causality of an AE, the event will be considered related to study therapy unless deemed otherwise by the DSMC.

8.2.3 Expectedness

The Investigator will be responsible for determining whether or not an adverse event was expected or unexpected. Expected adverse events are those adverse events that are listed or characterized in the Package Insert (PI) or current Investigator Brochure (IB). Unexpected adverse events are those not listed in the PI or current IB or not identified. This includes

adverse events for which the specificity or severity is not consistent with the description in the PI or IB. For example, under this definition, hepatic necrosis would be unexpected if the PI or IB only referred to elevated hepatic enzymes or hepatitis.

8.2.4 Action Taken and Outcome

Start and stop dates will be required for all adverse events and serious adverse events. The action taken in response to the event should also be recorded in the subject's research chart and corresponding eCRF. Event action terms include none, medication administered, non-drug therapy administered, surgery, hospitalization, or other with the option to specify. If a new medication is added the medication should also be added to the concomitant medications log.

All adverse events should be followed until stabilization or resolution. Event outcomes may be classified as resolved, resolved with sequelae, ongoing, or death.

8.2.5 Reporting Serious Adverse Events

All serious adverse events should be reported as soon as possible but no later than one business day after the Investigator becomes aware. All SAEs must be reported via the HCI CTMS (OnCore) and submitted to HCI-RCO@utah.edu. The HCI Clinical Site Monitor will in turn, submit the report to the Medical Monitor. The RCO will summarize and present all reported SAEs according to the Data and Safety Monitoring Plan at the monthly DSMC meeting.

At a minimum, initial SAE reports must include a description of the event, assessment of event causality, event grade, and the expectedness of the event. Although the Investigator may not know all the information at the time of the event, the available information should be reported. An SAE follow-up may be submitted at a later date once more information is known. It is required that follow-up reports be submitted until the SAE is resolved.

Follow-Up Information

It is recommended that follow-up reports be submitted as new information becomes available, however, a follow-up report should be submitted within 3 days of knowledge of event resolution. Follow-up information will be added to the SAE in OnCore and submitted to the DSMC via RCO.

8.2.6 FDA Notifications

This study will not hold an IND.

8.2.7 IRB Notification

The University of Utah IRB requires any unanticipated problems that may increase the risk to research participants be promptly reported. All study-therapy related, unexpected adverse events whose nature, severity, or frequency is not consistent with either:

- The unknown or foreseeable risk of adverse events that are described in the protocol related-documents, such as the IRB-approved research protocol, applicable investigator brochure, the current IRB-approved informed consent document, and/or other relevant sources of information, such as product labeling and package inserts; or

- The expected natural progression of any underlying disease or condition of the subject(s) experiencing the adverse event.

Adverse events meeting this criterion must be promptly reported to the IRB within 10 business days of awareness.

8.3 Special Situations

8.3.1 Pregnancy or Breastfeeding

Although pregnancy is not considered an adverse event, any exposure to the investigational products during pregnancy or breastfeeding must be reported promptly. Exposure may occur by a woman actively receiving study therapy or the partner of a male subject actively receiving study therapy becomes pregnant. Any possible pregnancy or breastfeeding exposure during study therapy and up to 30 days after the last dose of study therapy or up to the start of subsequent anticancer therapy (whichever happens first) must be reported within one business day of awareness regardless of the occurrence of an SAE. Should a woman on study therapy become pregnant, she should immediately discontinue study treatment.

Women exposed to IP during pregnancy or while breastfeeding will be followed for pregnancy outcome and neonate health. Pregnancy outcomes may meet criteria as an SAE if ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly occurs. Congenital anomalies that occur in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death should be reported as an SAE. Any neonatal deaths that occur up to 30 days after birth or breastfeeding exposure should be reported as an SAE. Further follow-up on birth outcomes and neonate health will be handled on a case-by-case base.

8.3.2 Hy's Law Cases

It is important to identify possible cases of Drug-Induced Liver Injury (DILI) early. Total bilirubin, AST, and ALT should be regularly monitored for elevations indicative of liver damage. Subjects who experience a transaminase elevation above three times the ULN should be monitored frequently to determine if the elevation is transient. Transient elevations are an indication of adaption and these subjects may be identified as "adaptors." However, should a transaminase elevation be followed by total bilirubin (TBili) increase, a DILI could be occurring. Any laboratory abnormalities meeting the following criteria should be reported within 24 hours of awareness:

- AST or ALT elevation > 3 x ULN; and
- Total bilirubin > 2 x ULN; and
- Absence of cholestasis; and
- No alternative explanation for the elevations (e.g., impaired glucuronidation capacity caused by genetic [Gilbert syndrome]; viral hepatitis A, B, or C, preexisting or acute liver disease; or another drug capable of causing the observed injury).

Investigators should conduct reasonable investigations to rule out other possible etiologies. Investigators should take into consideration the subject's use of ethanol, acetaminophen,

recreational drugs, herbal supplements, and medical history. A potential Hy's Law case will not be considered a confirmed case until all results and considerations have excluded alternative etiologies.

Possible cases of DILI will be promptly reported to the FDA prior to full work up to rule out other etiologies. Reporting should be completed on a MedWatch 3500A form and should include all available information, including the likelihood that the drug caused the event. Subjects should be closely followed until the resolution of the event.

8.4 Data Safety Monitoring Committee

A Data Safety Monitoring Committee (DSMC) at HCI is charged with ensuring the risk/benefit balance for subjects undergoing study therapy. The purpose of the DSMC is to ensure subject safety and make recommendations for study conduct to ensure subject safety and data integrity. The DSMC is chaired by a medical oncologist and may include, but is not limited to, representatives from medical oncology, oncological sciences, biostatistics, and pharmacy.

The roles and responsibilities of the DSMC are described in the NCI-approved Data and Safety Monitoring (DSM) plan. The activities of the committee include reviewing adverse events (including SAEs), deviations, important medical events, and approving cohort/dose escalations. Amendments that increase risk, increase treatment exposure, or impact study objectives will also be reviewed by the DSMC. If the DSMC and/or the PI have concerns about unexpected safety issues or AE trends, the study may be stopped and an unplanned safety data analysis may be conducted. Enrollment will not resume until the issues are resolved. The DSMC also reviews and approves audit reports generated by the Research Compliance Office.

All trials will be assigned and an oncologist member of the DSMC to serve as a medical monitor. In rare cases, an external medical monitor may be assigned. The Medical Monitor will be notified of all serious adverse events (SAEs). Specific notifications will also be issued when a dose-limiting toxicity is encountered and when the RP2D is defined. Approval from the Medical Monitor is required for all dose escalations. All serious adverse events (SAEs) occurring in subjects treated at HCI or its affiliates will also be reviewed by the full DSMC monthly.

Each trial is assigned a research compliance officer who will be responsible for monitoring the trial and reporting to the DSMC. The assessed risk level of the trial will determine the frequency with which monitoring occurs. The Research Compliance Officer monitor will review the study status and summarize enrollment, toxicities, SAEs, dose-escalation, statistical endpoints (e.g., stopping rules), deviations, and any other pertinent information for the full DSMC membership at the regularly scheduled meetings.

Audits will be conducted for all trials one year after enrollment begins and annually thereafter. Audits may be conducted more frequently as requested by the DSMC, Institutional Review Board (IRB), Protocol Review and Monitoring Committee (PRMC), Research Compliance Office management, or the Principal Investigator.

DSMC oversite will be tailored to the assessed risk level of the trial. Trials are categorized amongst three risk levels: high, moderate, and low.

This trial has been classified as high risk and therefore will be monitored by RCO and reviewed by DSMC after the first subject is enrolled and then quarterly thereafter.

9 STATISTICAL CONSIDERATIONS

9.1 Sample size determination

This is a descriptive study. The planned sample size is 12 enrolled subjects. For the study to be a success, at least 9 of 12 subjects must be consented, enrolled and complete the study. If at least 9 of 12 subjects complete the study, the lower bound of the 95% exact binomial confidence interval for the completion rate will exceed of 34%.

9.2 Population for Analyses

A modified intent-to-treat data set will be used for both safety and efficacy endpoint analysis. All subjects who have received one dose of study medication will be included in all efficacy and safety data sets. Subjects who fail to begin study therapy will be replaced.

9.3 Primary Endpoint

To assess the feasibility of recruiting, consenting, enrolling, and completing the study intervention for 12 patients.

Primary endpoint: The recruitment, consent, enrollment, and study completion of 12 patients. Study completion defined as participating in at least 2/3 of the 3 KAP sessions.

All subjects who enroll on the study will be considered evaluable. The completions rate will be reported along with a 95% exact binomial confidence interval (Clopper-Pearson method).

9.4 Secondary Endpoints

9.4.1 The frequency of adverse events (AEs) and serious adverse events (SAEs) characterized by type, severity (as defined by the NIH CTCAE, version 5.0), seriousness, duration, and relationship to study treatment.

All subjects who receive any study treatment will be included in the final summaries and listings of safety data. The detailed information collected for each AE will include a description of the event, duration, severity, relatedness to study drugs, action taken, and clinical outcome. The severity of the AEs will be graded according to the CTCAE v5.0. The statistical analysis of the safety data will be descriptive and tabular.

9.4.2 The proportion of screened patients that meet criteria on the Existential Distress Scale (EDS: Single domain ≥ 3 or total score ≥ 6).

All patients who have been consented to the study will be included in the final analysis.

The observed proportion will be reported along with a 95% exact confidence interval.

9.5 Exploratory Objectives

Exploratory endpoints include 1) the mean change in score on EDS and QIDS-SR-16 from baseline to 2 weeks post completion of intervention; 2) the correlation between total score on the MEQ-30 and NADA and change in the EDS score at the 2 week primary outcome time point;

and 3) the mean change in score on FACIT-Sp from baseline to Day 30 post completion of intervention.

An additional exploratory objective is to develop an algorithm with Storyline Health technology to rapidly discover the most predictive and information rich components in the assessment of burnout and its treatment response. The associated endpoints are 7) the identification of a behavioral phenotype that better predicts a response to ketamine intervention; and 8) the Storyline questionnaire completion rate.

Analysis of the above exploratory endpoints will be descriptive. Continuous variables will be summarized by the minimum, maximum, mean, standard deviation, and 95% confidence interval. The Storyline completion rate and 95% exact binomial confidence interval will be reported. Spearman rank correlation coefficients will be used to summarize the correlation between the total score on the MEQ-30 and NADA and change in the EDS score at the 2-week primary outcome time point.

10 ETHICAL AND REGULATORY CONSIDERATIONS

10.1 Human Subjects Protection

The study will be conducted in accordance with the protocol, 21 CFR, HIPAA regulations, the Belmont Principles, ICH Guidelines for Good Clinical Practice (GCP), and the Declaration of Helsinki. Informed consent will be obtained from all research participants or their legally authorized representative before performing any study procedures using the most recent IRB approved version.

10.1.1 Personal Data Protection

All parties will take all necessary actions required for the protection of subject personal data. Subjects enrolled in the study will be assigned a subject number and will be reference by this number. Directly identifiable data will be omitted from reports, publications, and other disclosures. All personal data will be store at the study site in encrypted electronic and/or paper form stored in a locked and secured facility. The site will be responsible for maintaining a list of subjects linking each subject with their subject number. Data will only be accessed by appropriate personnel and will be password protected or securely stored in a locked room. In the case of a potential breach of personally identifiable data, the site will take responsibility to ensure appropriate action is taken according to institutional practice and applicable laws and regulations.

10.2 Institutional Review

Before the initiation of the study, the Investigator will have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, (e.g., recruitment advertisements, questionnaires, if applicable), from the IRB. All correspondence with the IRB should be retained in the Investigator's regulatory file. Changes to the protocol or approved documents may not be made until IRB approval has been received.

However, if a change is necessary to eliminate immediate hazards to the subjects, prospective approval is not necessary.

The investigator or designee should provide the IRB with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

10.3 Investigator Responsibilities

The Investigator is responsible for ensuring the trial is conducted in compliance with the current IRB approved version of the protocol, GCP, the Declaration of Helsinki, and any applicable national and local laws and regulations.

10.4 Protocol Amendments

Any amendments or administrative changes to an IRB approved protocol will not be initiated without submission of an amendment for IRB review and approval. However, prospective IRB approval will not be sought when an amendment is required to eliminate immediate risk to subjects on study. In these cases, amendments will be retrospectively submitted to the IRB for review and approval.

Any amendments to the protocol that significantly affect the safety of subjects, the scope of the investigation, or the scientific quality of the study will be submitted to the FDA for review.

10.5 Protocol Deviations

A deviation will be defined as any noncompliance with ICH GCP or the clinical protocol requirements. The noncompliance may be either on the part of the participant, the Investigator, or the study staff. As a result of the deviation, a corrective action must be implemented to ensure future deviation does not occur. It is the Investigator's responsibility to identify and report deviations from ICH GCP or protocol requirements. These deviations and corrective action should be documented in the subject's research chart, the associated eCRF, and reported to the IRB per their policy.

10.6 FDA Reporting

This study will not hold an IND.

11 DATA HANDLING

11.1 Recording and Collection of Data

Primary source documentation will come directly from the subject's medical record. All source documentation should be attributable, legible, contemporaneous, original, accurate, complete, and available. All documentation should be signed and dated by applicable personnel. Relevant source data will be transcribed into the electronic case report forms (eCRFs) and should be completed as soon as possible after data availability. The eCRFs will be part of a computerized database grounded in the protocol requirements and study objectives. The database will be designed to comply with 21 CFR Part 11.

The Investigator has ultimate responsibility for ensuring that all data collected and recorded is accurate and consistent. He/she will need to sign off on all eCRFs to attest that all data recorded on them is true. A separate screening log of all the subjects screened for participation in the study must also be maintained and should include gender, age, eligibility status, the reason for ineligibility (if applicable), and study allocated subject number (if applicable).

11.1.1 Storyline Health Data Confidentiality and Security

The individuals who can view participant videos will only include the participant and the University of Utah and Storyline Health researchers involved in the study. Participant videos will never be shared with individuals outside of the study.

All study videos will be collected and stored in the Storyline Health Vault Database, which is an ultra-secure, cloud based data storage platform specially designed for protecting participant videos and related data. It has the following technical features that will protect all data for the study:

11.1.1.1 *HTTPS Communication Protocol*

All Storyline participant data is transferred and accessed in an encrypted and secure manner. The Storyline Health database API is only available on port 443 via HTTPS and their public websites force HTTPS with HSTS. This is the most secure system available and prevents unauthorized access.

11.1.1.2 *Access Management*

No one else can access participant data other than the participant and researchers involved in the study. Storyline Health ensures this by maintaining robust defense at each layer of the platform to secure data. The features include immutable audit logs, restrictive network rules, and per-record encryption, which all prevent unauthorized access to personal data.

11.1.1.3 *Encryption / Decryption*

All participant records are encrypted with 256-bit AES encryption keys as soon as they enter Storyline Health's infrastructure. Every record is encrypted with a unique initialization vector by a unique encryption key to achieve semantic security. Storyline verifies each record's integrity on a regular basis and on each record request using a hash-based authentication code (HMAC) calculated using its own unique 256-bit HMAC key. Encryption keys, initialization vectors and HMAC keys are re-keyed and each record re-encrypted on a regular basis.

11.1.1.4 *Network Security*

Multiple subsystems combine to power Storyline Health and secure your data. Each subsystem is totally and completely segmented from one another by software and network security rules to maximize protection. Storyline does not store encrypted records and their encryption keys in the same server cluster. Each subsystem can only be accessed by another subsystem via specific network routes and specific inbound and outbound port rules. These features make Storyline’s system ultra-secure for participant data storage.

Participant videos only exist within the ultra-secure Storyline Health system, where individual participants will have access to their own data and have control over them. The videos will not be stored on their smartphone, tablet or personal computer, or on any other vulnerable device

(such as a researcher laptop). The Storyline Health platform ensures that video data is never left on a device that can be lost or stolen.

Participants will be given ownership of their data. The Storyline Health platform will make it easy for individual participants to view and delete their videos at any time if they choose. If they choose to delete a video, they will be informed about the impact on the study, the importance of their contributions and the major privacy protection measures in place and confidentiality rules governing their data.

Any facial or speech micro-features extracted from participant videos using artificial intelligence and other data mining approaches will be stored in specially designed, de-identified Storyline Health StoryARC formatted files that maintain participant confidentiality. StoryARC files are text files containing letters and numbers that detail measures extracted from the videos and enable researchers to analyze study participant behavior patterns using mathematical approaches without revealing participant identity or personal information

11.2 Data Management

To accommodate evaluations, inspections, and/or audits from regulatory authorities, the Investigator must maintain all study records including subject identity, source documentation, original signed consent form, safety reporting forms, monitoring logs, IP accountability records, relevant correspondence (e.g., letters, emails, meeting minutes, etc.), and any other documents pertaining to the conduct of the study. The Investigator must also agree to the maintain source documents for a minimum of two years after regulatory approval of the investigational product per 21 CFR 312.57. For the duration of record maintenance, records must be stored in a secure location and protected from the elements.

12 PUBLICATION PLAN

In accordance with U.S. regulations and the best interest of research ethics and transparency, this study will be registered on ClinicalTrials.gov before subject enrollment. US Basic Results will also be reported and available on ClinicalTrials.gov within one year of the primary completion date, regardless of formal journal publication. All results will be reported objectively, accurately, balanced, and completely, regardless of the study outcome.

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Appendix 1: ECOG Performance Status[12]

Score	Definition
0	Fully active, able to carry on all pre-disease activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hour
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Confined to bed or chair
5	Dead

Appendix 2: Existential Distress Scale (EDS)

We would like to better understand how you're feeling so that we can be more helpful to you. We would like to ask you some questions about some distressing thoughts that people with cancer may worry about. These questions are about whether you have been feeling badly about yourself or feeling lonely, and whether you have been questioning the sense of meaning in your life. Please tell us if you have been distressed by any of these concerns and if so, how much distress you have been experiencing.

How distressed have you been by the thought:

	Not distressed	Mildly distressed	Moderately distressed	Greatly distressed	Unbearably distressed
1. That you are all alone?	0	1	2	3	4
2. That no one will miss you when you are gone?	0	1	2	3	4
3. That no one cares about you?	0	1	2	3	4
4. That you are or will be a burden to others?	0	1	2	3	4
5. That you have nothing to offer others?	0	1	2	3	4
6. That you don't matter?	0	1	2	3	4
7. That you are worthless?	0	1	2	3	4
8. That your life is empty?	0	1	2	3	4
9. That your life is meaningless?	0	1	2	3	4
10. That you have nothing to live for?	0	1	2	3	4

_____ _____

Participant Signature Date

_____

Study ID

Appendix 3: Quick Inventory of Depressive Symptomatology (QIDS-SR-16)

Please circle the one response to each item that best describes you for the past seven days.

1. Falling Asleep:

   0 I never take longer than 30 minutes to fall asleep.
   1 I take at least 30 minutes to fall asleep, less than half the time.
   2 I take at least 30 minutes to fall asleep, more than half the time.
   3 I take more than 60 minutes to fall asleep, more than half the time.

2. Sleep During the Night:

   0 I do not wake up at night.
   1 I have a restless, light sleep with a few brief awakenings each night.
   2 I wake up at least once a night, but I go back to sleep easily.
   3 I awaken more than once a night and stay awake for 20 minutes or more, more than half the time.

3. Waking Up Too Early:

   0 Most of the time, I awaken no more than 30 minutes before I need to get up.
   1 More than half the time, I awaken more than 30 minutes before I need to get up.
   2 I almost always awaken at least one hour or so before I need to, but I go back to sleep eventually.
   3 I awaken at least one hour before I need to, and can't go back to sleep.

4. Sleeping Too Much:

   0 I sleep no longer than 7–8 hours/night, without napping during the day.
   1 I sleep no longer than 10 hours in a 24-hour period including naps.
   2 I sleep no longer than 12 hours in a 24-hour period including naps.
   3 I sleep longer than 12 hours in a 24-hour period including naps.

5. Feeling Sad:

   0 I do not feel sad
   1 I feel sad less than half the time.
   2 I feel sad more than half the time.
   3 I feel sad nearly all of the time.

6. Decreased Appetite:

   0 There is no change in my usual appetite.
   1 I eat somewhat less often or lesser amounts of food than usual.
   2 I eat much less than usual and only with personal effort.
   3 I rarely eat within a 24-hour period, and only with extreme personal effort or when others persuade me to eat.

7. Increased Appetite:

   0 There is no change from my usual appetite.
   1 I feel a need to eat more frequently than usual.
   2 I regularly eat more often and/or greater amounts of food than usual.
   3 I feel driven to overeat both at mealtime and between meals.

8. Decreased Weight (Within the Last Two Weeks):

   0 I have not had a change in my weight.
   1 I feel as if I've had a slight weight loss.
   2 I have lost 2 pounds or more.
   3 I have lost 5 pounds or more.

9. Increased Weight (Within the Last Two Weeks):

   0 I have not had a change in my weight.
   1 I feel as if I've had a slight weight gain.
   2 I have gained 2 pounds or more.
   3 I have gained 5 pounds or more.

10. Concentration/Decision Making:

   0 There is no change in my usual capacity to concentrate or make decisions.
   1 I occasionally feel indecisive or find that my attention wanders.
   2 Most of the time, I struggle to focus my attention or to make decisions.
   3 I cannot concentrate well enough to read or cannot make even minor decisions.

11. View of Myself:

   0 I see myself as equally worthwhile and deserving as other people.
   1 I am more self-blaming than usual.
   2 I largely believe that I cause problems for others.
   3 I think almost constantly about major and minor defects in myself.

12. Thoughts of Death or Suicide:

   0 I do not think of suicide or death.
   1 I feel that life is empty or wonder if it's worth living.
   2 I think of suicide or death several times a week for several minutes.
   3 I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life.

13. General Interest:

   0 There is no change from usual in how interested I am in other people or activities.
   1 I notice that I am less interested in people or activities.
   2 I find I have interest in only one or two of my formerly pursued activities.
   3 I have virtually no interest in formerly pursued activities.

14. Energy Level:

0 There is no change in my usual level of energy.
1 I get tired more easily than usual.
2 I have to make a big effort to start or finish my usual daily activities (for example, shopping, homework, cooking or going to work).
3 I really cannot carry out most of my usual daily activities because I just don't have the energy.

15. Feeling Slowed Down:

0 I think, speak, and move at my usual rate of speed.
1 I find that my thinking is slowed down or my voice sounds dull or flat
2 It takes me several seconds to respond to most questions and I'm sure my thinking is slowed.
3 I am often unable to respond to questions without extreme effort.

16. Feeling Restless:

0 I do not feel restless.
1 I'm often fidgety, wringing my hands, or need to shift how I am sitting.
2 I have impulses to move about and am quite restless.
3 At times, I am unable to stay seated and need to pace around.

To Score:

1. Enter the highest score on any 1 of the 4 sleep items (1-4) _____
2. Item 5 _____
3. Enter the highest score on any 1 1 appetite/ weight item (6-9) _____
4. Item 10 _____
5. Item 11 _____
6. Item 12 _____
7. Item 13 _____
8. Item 14 _____
9. Enter the highest score on either of the 2 psychomotor items (15 and 16) _____

TOTAL SCORE (Range 0–27) _____

_____ _____
Participant Signature Date

_____
Study ID

Appendix 4: Columbia-Suicide Severity Rating Scale (C-SSRS) Baseline/Screening

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

_____ _____

Interviewer Signature Date

_____

Study ID

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it… and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐

INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** ____ ***Type # (1-5)*** ____ ***Description of Ideation*** Past X Months - ***Most Severe Ideation:*** ____ ***Type # (1-5)*** ____ ***Description of Ideation***	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

Appendix 5: Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Visit

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

_____ _____

Interviewer Signature Date

_____

Study ID

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	**Most Severe**
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

Appendix 6: FACIT-Sp (Version 4)

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

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACIT-Sp (Version 4)

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

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACIT-Sp (Version 4)

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

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
Sp1	I feel peaceful	0	1	2	3	4
Sp2	I have a reason for living	0	1	2	3	4
Sp3	My life has been productive	0	1	2	3	4
Sp4	I have trouble feeling peace of mind	0	1	2	3	4
Sp5	I feel a sense of purpose in my life	0	1	2	3	4
Sp6	I am able to reach down deep into myself for comfort	0	1	2	3	4
Sp7	I feel a sense of harmony within myself	0	1	2	3	4
Sp8	My life lacks meaning and purpose	0	1	2	3	4
Sp9	I find comfort in my faith or spiritual beliefs	0	1	2	3	4
Sp10	I find strength in my faith or spiritual beliefs	0	1	2	3	4
Sp11	My illness has strengthened my faith or spiritual beliefs	0	1	2	3	4
Sp12	I know that whatever happens with my illness, things will be okay	0	1	2	3	4

_____ _____

Participant Signature Date

_____

Study ID

Appendix 7: Nondual Awareness Dimensional Assessment (NADA)

NONDUAL AWARENESS DIMENSIONAL ASSESSMENT – STATE

Please read each statement and indicate the extent to which you agree with each statement. In other words, how well does the statement describe what you just experienced, just now?	**Not at all**										**Very much**
1. I experienced all things seeming to unify into a single whole.	0	1	2	3	4	5	6	7	8	9	10
2. I experienced all sense of self and identity dissolve away.	0	1	2	3	4	5	6	7	8	9	10
3. I felt surrounded and filled with a blissful warmth or energy.	0	1	2	3	4	5	6	7	8	9	10

NADA-S SCORING

Full Scale Score: Average all items.

_____ _____

Participant Signature Date

_____

Study ID

Appendix 8: Mystical Experiences Questionnaire (MEQ-30)

Instructions: Looking back on the entirety of your session, please rate the degree to which at any time during that session you experienced the following phenomena. Answer each question according to your feelings, thoughts, and experiences at the time of the session. In making each of your ratings, use the following scale:

0 – none; not at all

1 – so slight cannot decide

2 – slight

3 – moderate

4 – strong (equivalent in degree to any other strong experience)

5 – extreme (more than any other time in my life and stronger than 4)

_____ 1. Loss of your usual sense of time.

_____ 2. Experience of amazement.

_____ 3. Sense that the experience cannot be described adequately in words.

_____ 4. Gain of insightful knowledge experienced at an intuitive level.

_____ 5. Feeling that you experienced eternity or infinity.

_____ 6. Experience of oneness or unity with objects and/or persons perceived in your surroundings.

_____ 7. Loss of your usual sense of space.

_____ 8. Feelings of tenderness and gentleness.

_____ 9. Certainty of encounter with ultimate reality (in the sense of being able to “know” and “see” what is really real at some point during your experience.

_____ 10. Feeling that you could not do justice to your experience by describing it in words.

_____ 11. Loss of usual awareness of where you were.

_____ 12. Feelings of peace and tranquility.

_____ 13. Sense of being “outside of” time, beyond past and future.

_____ 14. Freedom from the limitations of your personal self and feeling a unity or bond with what was felt to be greater than your personal self.

_____ 15. Sense of being at a spiritual height.

_____ 16. Experience of pure being and pure awareness (beyond the world of sense impressions).

_____ 17. Experience of ecstasy.

_____ 18. Experience of the insight that “all is One”.

_____ 19. Being in a realm with no space boundaries.

_____ 20. Experience of oneness in relation to an “inner world” within.

_____ 21. Sense of reverence.

_____ 22. Experience of timelessness.

_____ 23. You are convinced now, as you look back on your experience, that in it you encountered ultimate reality (i.e., that you “knew” and “saw” what was really real).

_____ 24. Feeling that you experienced something profoundly sacred and holy.

_____ 25. Awareness of the life or living presence in all things.

_____ 26. Experience of the fusion of your personal self into a larger whole.

_____ 27. Sense of awe or awesomeness.

_____ 28. Experience of unity with ultimate reality.

_____ 29. Feeling that it would be difficult to communicate your own experience to others who have not had similar experiences.

_____ 30. Feelings of joy.

_____ _____
Participant Signature Date

_____
Study ID

Appendix 9: Death and Dying Distress Scale (DADDS)

Having cancer can bring to mind thoughts and feelings about life and death. Listed below are several thoughts or concerns that some people with cancer may think about, at any stage of their disease.

Please tell us how distressed you felt over the past 2 weeks about each item listed below. By distress, we refer generally to negative feelings such as being angry, afraid, sad, or anxious.

If you have many different negative feelings about an item, choose your answer based on the strongest negative feeling that you've had. Please circle only one number per line.

0 = I was not distressed about this thought or concern.
1 = I experienced very little distress.
2 = I experienced mild distress.
3 = I experienced moderate distress.
4 = I experienced great distress.
5 = I experienced extreme distress.

Over the past 2 weeks, how distressed did you feel about:

1. Not having done all the things that I wanted to do.	0	1	2	3	4	5
2. Not having said all that I wanted to say to the people I care about.	0	1	2	3	4	5
3. Not having achieved my life goals and ambitions.	0	1	2	3	4	5
4. Not knowing what happens near the end of life.	0	1	2	3	4	5
5. Not having a future.	0	1	2	3	4	5
6. The missed opportunities in my life.	0	1	2	3	4	5
7. Running out of time.	0	1	2	3	4	5
8. Being a burden to others.	0	1	2	3	4	5
9. The impact of my death on my loved ones.	0	1	2	3	4	5
10. My own death and dying.	0	1	2	3	4	5

Over the past 2 weeks, how distressed did you feel that your own death and dying may:

11. Happen suddenly or unexpectedly.	0	1	2	3	4	5
12. Be prolonged or drawn out.	0	1	2	3	4	5
13. Happen when I am alone.	0	1	2	3	4	5
14. Happen with a lot of pain or suffering.	0	1	2	3	4	5
15. Happen very soon.	0	1	2	3	4	5