LTAS	Long-term AIDS Survivor
MAIA	Multidimensional Assessment of Interoceptive Awareness
MAOI	Monoamine Oxidase Inhibitors
MEQ-30	Mystical Experience Questionnaire—30
MOCA	Montreal Cognitive Assessment
MQoL-RS	McGill Quality of Life Questionnaire—Revised-Short
NR	Nature Relatedness Scale, Short Form
NEO-PI-R	Revised NEO Personality Inventory
OPLH	Older People Living with HIV
PA-SEGT	Psilocybin-assisted Supportive-Expressive Group Therapy
PCL-5	PTSD Checklist
PEQ-S	Persisting Effects Questionnaire—Spirituality
PLH	People Living with HIV
Plt	Platelet
PPSv2	Palliative Performance Scale version 2
PTG	Post-Traumatic Growth
PTGI-SF	Post-Traumatic Growth Inventory—Short Form
PTSD	Post-Traumatic Stress Disorder
QoLLTI-Fv2	Quality of Life in Life-Threatening Illness—Family Carer Version 2
SAHD	Schedule of Attitudes towards Hastened Death
SCID-5-PD	Structured Clinical Interview for DSM-5 Personality Disorders
SCID-5	Structured Clinical Interview for DSM-5
SCS-R	Social Connectedness Scale-Revised
SEGT	Supportive-Expressive Group Therapy
SEGT-TG	Supportive-Expressive Group Therapy Topic Grid
SNRI	Serotonin-Norepinephrine Reuptake Inhibitors
SSRI	Serotonin Reuptake Inhibitors
STAI	State-Trait Anxiety Inventory
Tbili	Total bilirubin
TCA	Tricyclic Antidepressants
TProt	Total protein
TSH	Thyroid Stimulating Hormone
WBC	White Blood Cell

- Change in ART medication adherence will be defined as the difference in pre-treatment, post-treatment, and 3-month follow-up mean scores of the ART Medication Adherence Scale.

- Change in depression will be defined by the difference in pre-treatment, post-treatment, and 3-month follow-up mean scores of the Center for Epidemiologic Studies Depression Scale—Revised.

- Change in subject quality of life will be defined by the difference in pre-treatment, post-treatment, and 3-month follow-up mean scores of the McGill Quality of Life Questionnaire—Revised.

- Change in desire for hastened death will be defined as the difference in pre-treatment, post-treatment, and 3-month follow-up mean scores of Schedule of Attitudes towards Hastened Death.

- Change in anxiety will be defined as the difference in pre-treatment, post-treatment, and 3-month follow-up mean scores of the State-Trait Anxiety Inventory.

- Change in social support will be defined as the difference in pre-treatment, post-treatment, and 3-month follow-up mean scores of the Duke/UNC Functional Social Support Questionnaire-5.

- Post-traumatic growth due to the intervention will be defined by post-treatment and 3-month follow-up mean scores of Post-Traumatic Growth Inventory—Short Form.

- Change in PTSD symptoms will be defined as the difference in pre-treatment, post- treatment, and 3-month follow-up mean scores of the PTSD Checklist-5.

- Change in global clinical status will be defined as the difference in pre-treatment and post- treatment mean scores of the Clinical Global Impressions Scale completed by a clinical rater.

- Change in openness to experience will be defined as the difference in pre-treatment, post-treatment, and 3-month follow-up mean scores of the International Personality Item Pool—Openness to Experience-20 scale.

- Change in mindfulness will be defined as the difference in pre-treatment, post-treatment, and 3-month follow-up mean scores of subscales of the Multidimensional Assessment of Interoceptive Awareness.

- Change in social connectedness will be defined by the difference in pre-treatment, post-treatment, and 3-month follow-up mean scores of the Social Connectedness Scale—Revised.

- Change in Nature Relatedness will be defined by the difference in pre-treatment, post-treatment, and 3-month follow-up mean scores of the Nature Relatedness Scale, Short Form Version.

- Change in alcohol and drug use will be defined by different in the baseline and 3-month follow-up AUDIT and DUDIT scores

Psychotherapeutic process and mechanisms will be explored with the following endpoints:

- Change in group cohesion will be defined as the difference in rate of Group Questionnaire score change pre- and post-psilocybin.

stabilizers. Low dose (≤50mg) TCAs prescribed for neuropathic pain are not considered psychotropic; participants are prohibited from using these medications during the study, but do not need to demonstrate a period of psychiatric stability for 2 weeks prior to enrollment. Patients will be asked to refrain from consuming alcohol, prescription analgesics, PRN anxiolytics and PRN stimulants the day before and of a psilocybin session.

7. History of a psychotic disorder or Bipolar disorder I or II (determined by SCID-5).
8. Family history of primary psychotic disorder or primary bipolar disorder (first or second degree relative).
9. Current, severe Major Depressive Episode (These individuals will be referred to standard-of-care treatment in the community).
10. History of active suicidal ideation with intent in the last 3 months (Suicidal ideation score >3 and Reason for ideation >1 on C-SSRS); or a history of suicide attempt in the last 2 years with Actual lethality/Medical damage >0 or Potential lethality >0 (on C-SSRS).
11. Narcissistic personality disorder, moderate-to-severe (determined by SCID-5-PD).
12. History of Hallucinogen Use Disorder (Moderate or Severe) or Hallucinogen Persisting Perception Disorder (determined by SCID-5).
13. History of a seizure disorder in adulthood.
14. CNS metastases or symptomatic CNS infection.
15. Clinically significant cardiovascular disease (CAD, CHF, arrhythmia); or baseline QT/QTc>500msec; or baseline QT/QTc 451-500msec with repeat QT/QTc >500msec.
16. Uncontrolled hypertension (SBP>139mmHG or DBP>89mmHG if over 65 years old) or tachycardia (average HR>90bpm if over 65 years old) averaged over at least two measurements.
17. Supplemental oxygen requirement.
18. Poorly controlled diabetes mellitus (e.g., history of an episode of hypoglycemia or hospitalization for hyperglycemia on the current diabetes regimen).
19. Inadequate hepatic function (Total bilirubin >2mg/dL, OR AST >6 upper institutional upper limit of normal, OR AST >6 upper institutional upper limit of normal), as determined by most recent laboratory tests.
20. Inadequate renal function as determined by eGFR < 30 mL/min/1.73 m2 (based on the MDRD equation) or CrCl < 30 mL/min (based on the C-G equation).
21. Concomitant dosing of psilocybin with known UGT1A10 and UGT1A9 inhibitors (e.g., diclofenac and probenecid) will be avoided. There is *no* exclusion criterion based on the use of medications or substances that are inhibitors or inducers of CYP450 enzymes.
22. The use of efavirenz (a.k.a, Sustiva or Atripla).
23. If deemed by clinical judgment of the study investigators to be unsafe for undergoing the intervention and/or inappropriate for participating in a therapy group.

3.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for 8 weeks or until:

- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patients decides to withdraw from the study
- Significant patient non-compliance with protocol
- General or specific changes in the patients' condition render the patient unacceptable for further treatment in the judgment of the investigator.

3.5 Duration of Follow Up

Patients will be followed for 3 months after completion of treatment or removal from study, or

techniques, integrative medicine modalities, other.

Credibility/Expectancy Questionnaire (CrEQ)—A 6-item self-report measure of cognitive and affective assessments of a mental health therapy with high internal consistency and good test-retest reliability [162] that we have adapted for psychological distress.

Demoralization Scale-II (DS-II)—An abbreviated, 16-item and 3-point version of the well-validated original 24-item Demoralization Scale [163], which is the most widely used self-report measure of demoralization in palliative care patients [29]. The DS-II has two subscales: Meaning and Purpose, and Distress and Coping Ability, and shows both good internal and external validity in palliative care patients [27, 164].

Drug Use Disorders Identification Test (DUDIT) – An 11-item screening tool developed as a parallel to the AUDIT to assess drug consumption, drug use behaviors, and drug-related problems.

Duke UNC Functional Social Support Questionnaire-5 (DUFSS-5)—A 5-item, 3-point Likert, self-report measure of perceived functional social support. The abbreviated 5-item scale has been validated in patients with severe medical illness (advanced cancer or AIDS) [165].

Experiences in Close Relationships scale—Modified 16 (ECR-M16)—A 16-item, 7-point Likert self-report measure of attachment security. The abbreviated 16-item version is reliable and has been validated in patients with severe medical illness (metastatic cancer) [166].

Group Questionnaire (GQ)—A validated self-report 30-item 7-point Likert questionnaire of therapeutic relationships in group therapy [133]. GQ has a three-factor model of group cohesion: Positive Bonding, Positive Working, Negative Relationships, all of which manifest in both member-member and member-leader relationships [167]. GQ was empirically-derived from measures in the AGPA CORE-R Battery [139] that assess therapeutic alliance and cohesion—the two factors known to best predict clinical outcomes of group psychotherapy trials [132].

Group Psychotherapy Intervention Rating Scale (GPIRS)—An empirically-derived observer-rated 48-item instrument that assesses group therapist behaviors that help create and maintain group cohesion [168].

HIV and Abuse Related Shame Inventory (HARSI)—A validated 22-item 5-point Likert scale (“Not at All” to “Very Much”) [169].

Hill Interaction Matrix (HIM)—The gold standard in group therapy process measures [170], the HIM is an observer-rated instrument that assesses group therapy sessions using a 4x4 matrix of style categories (conventional, assertive, speculative and confrontational) and content categories (general, group, personal, relationship). The HIM has been used since the 1960s and there exists an extensive database of normative data against which to compare outcomes [134].

International Personality Item Pool-Openness to Experience-20 (IPIP-OE-20)—A 20-item self-report measure that uses items in the public domain to evaluate a construct approximately equivalent to Openness, which is evaluated by the NEO-PI-R [171].

Inventory of Complicated Grief (ICG)—A well-validated 19-item 5-point Likert scale (“never” to “always”) that is the gold standard self-report instrument for measuring complicated grief [172, 173].

Life Event Checklist—5 (LEC5)—A 17-item self-report screening measure of different categories of potentially traumatic events that have occurred over the respondent’s

therapy sessions and document the number of minutes in which particular target discussion topics are handled in the session.

Structured Clinical Interview for DSM-5 (SCID-5)—The gold standard structured clinical interview for DSM-5 criteria for major psychopathology. We will use portions of the SCID to screen for lifetime Depressive, Psychotic, Bipolar and Hallucinogen-related disorders.

Structured Clinical Interview for DSM-5 Personality Disorders (SCID-5-PD)—A self-report questionnaire based on DSM-5 criteria for personality disorders. We will use this to screen for Cluster B personality disorders.

6.3 Qualitative Analyses

Qualitative analyses be grounded in Interpretive Phenomenological Analysis (IPA) [184]. Data for qualitative analysis will include transcripts from a convenience sample of group therapy sessions and psilocybin drug sessions, therapist process notes, patients' written accounts of their psilocybin experiences, verbal feedback elicited from patients throughout the study, transcripts from focus groups conducted after the study endpoint, and transcripts from 30-to-60-minute semi-structured interviews conducted with selected patients after the 3-month follow-up. IPA is widely used in studies of psychological interventions to better understand a patient's experience of their treatment, and is typically used to elicit convergent and divergent themes in studies with small sample sizes [184]. Two investigators with experience in qualitative analysis will at first independently code the same transcripts for prominent themes, followed by comparison of their codes until a consensus is reached on an appropriate coding scheme. A code book will be established which will be used to code further sources. Consensus will be re-established on an iterative basis according to the criteria of the coders and the PI.

6.4 Schedule of Procedures and Observations

The study-specific assessments are detailed in this section and outlined in Section 6 Schedule of Study Procedures and Assessments. Screening assessments will be performed on enrollment. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. All on-study visit procedures are allowed a window of ± 7 days unless otherwise noted. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

6.4.1 Phone Screening

Potential subjects will be screened over the phone to assure that they understand the time requirements of the study, they are at least 50 years old, they were diagnosed with HIV prior to the clinical availability of combination antiretroviral therapy (~1996), they report experiencing moderate-to-severe symptoms of demoralization on the DS-II, and that they do not meet any major exclusion criteria (e.g., history of psychosis or bipolar disorder; recent active suicidal ideation). They will also be screened for complicated grief on the ICG to better characterize their clinical appropriateness for the study. A brief orientation to the study protocol, including psychoeducation on psilocybin, will be provided to patients who are not excluded. The patient will then be scheduled for an in-person screening and enrollment visit.

6.4.2 In-person Screening and Enrollment

Screening procedures and assessments to be completed on day of Enrollment (prior laboratory results may be considered instead of performing labs at enrollment if the results are less than 1 month old):

- Informed Consent Form and HIPPA form. Participants will be provided with a printed version of the study brochure.
- Demographics questionnaire (Age, ethnicity/race, civil status, years of education, income)
- Vital signs; Physical examination; Mental Status Exam; Complete medical and psychiatric history, including current medication list; Performance status (PPSv2); Cognitive Status (Montreal Cognitive Assessment)
- Complete blood count (WBC, Hgb, Hct, Plt)
- Comprehensive metabolic panel (Na, K, Cl, CO2, BUN, Cr, Gluc, Tbili, Ast, Alt, AlkPhos, TProt, Alb)
- TSH, FT4
- CRP
- Urinalysis
- Urine beta-hCG, when applicable (must be completed on day of Enrollment)
- Urine toxicology (must be completed on day of Enrollment)
- HIV viral load, CD4 count, CD8 count
- RPR or Treponemal Antibody
- Electrocardiogram (ECG)
- Selected screening portions of Structured Clinical Interview for DSM-5 Clinical Trials Version (SCID-5); sections on current Depressive disorders; lifetime Psychotic disorders, Bipolar disorders and Hallucinogen-related disorders), Structured Clinical Interview for DSM-5 Personality Disorders (SCID-5-PD) section on Cluster B disorders.
- Columbia Suicide Severity Rating Scale (C-SSRS): Baseline/Screening (last 12 months)
- ART Medication Adherence Scale (AMAS), Centers for Epidemiologic Studies Depression Scale—Revised (CESD-R), Demoralization Scale—II (DS-II), Inventory of Complicated Grief (ICG), McGill Quality of Life Questionnaire-Revised-Short (MQoL-RS), Life Event Checklist—5 (LEC5), PTSD Checklist-5 (PCL-5), Schedule of Attitudes towards Hastened Death (SAHD), State-Trait Anxiety Inventory (STAI).
- Clinical interview of about 45 minutes duration to discuss details about the subject's personal life, such as past and current relationships, family dynamics, and concerns about their disease.
- Eligible subjects will be placed on the waitlist until 6 subjects are available to start a group.
- Subjects who score high on the SCID-5-PD dimensional scale for Borderline Personality Disorder and are enrolled in the study will be monitored closely during the trial and study clinicians will consider offering them an individual therapy visit around the time that the subacute beneficial effects of psilocybin are expected to wear off (about 10 days post exposure) if the subjects appear unusually distressed at that time.

6.4.3 Baseline Assessments (Week 0)

6.4.3.1 Baseline Subject Assessments

Baseline assessments will be filled out during an individual therapy session wherein the subject will meet one or both of the group therapists in the week prior to the first group therapy session. Separately, the subject's caregiver/important other will be invited to meet with study staff for a brief interview on their relationship with the subject [see Appendix C for interview guides]. The individual session for the study subject is meant to build trust and rapport with the group therapists, to learn more about the subject's life history and struggles with his/her health, to elicit the subject's preferences and intentions for the treatment sessions, and to orient the subject further to the intervention protocol. If screening/enrollment measures were completed within 1 week of the baseline assessment, those measures will not need to be repeated.

- AMAS, AUDIT, CESD-R, CTC, DS-II, DUDIT, DUFSS-5, ECR-M16, ICG, IPIP-OE-20, MAIA-R, MQoL- RS, NR-6, PCL-5, PTGI-SF, SAHD, SCS-R, and STAI. A clinical rater will perform a CGI and C-SSRS(Interval) for each subject.

6.4.3.2 Baseline Caregiver/Important Other Assessments

- CORF

6.4.4 Treatment Period

6.4.4.1 Group Therapy Sessions #1-4 (Weeks 1-2)

Patients will undergo four 90-minute group therapy preparatory sessions (2 per week) that will be audio and video recorded. Video footage of a random sampling of sessions will be analyzed with the HIM, SEGT-TG and the GPIRS. Patients will fill out the GQ after the sessions in Week 2 and 4. Women of child-bearing potential will provide a urine sample for a urine beta-hCG at Group Therapy visit #4. A clinical rater will administer the C- SSRS(Interval) to each subject at each weekly study visit.

6.4.4.2 Individual Drug Sessions (Week 3)

Patients will undergo individual drug sessions in which they are administered psilocybin 0.30mg/kg (or 0.36mg/kg) po, with a maximum dose not to exceed that calculated for a BMI of 35 at their height. The drug will be administered following the safety guidelines outlined by Johnson et al [24].

The day prior to the session, patients will be screened over the phone for contraindicated medications and reminded about procedures for the medication visit. ***Specifically, participants will be reminded that they cannot drive an automobile for the rest of the day after their medication visit, and they will be advised that if they will take the BART, they should not drive their car to the BART station.***

On the day of the medication visit, patients will arrive at the Langley Porter Psychiatric Institute around 08:00 and be oriented to the drug session room, which will contain a couch for the patient to lie on and aesthetically pleasing décor. Before the medication session starts, participants will complete a urine drug screen and the CrEQ. Patients will also undergo a blood draw at the Clinical Research Service for the following tests: CBC, CMP, and CRP. Participants will then return to the study room and hand over their shoes, keys, wallet and phones to the study therapists for safe keeping; these will all be returned to the patient upon completion of the treatment session.

The entire session will be audio and video recorded for subsequent behavioral analysis and

rating of therapist adherence to the therapy protocol. Participants have the option of requesting that AV recording be turned off momentarily if they will to discuss material they feel is too personal to be recorded.

During the drug session, vital signs (heart rate and blood pressure) will be recorded at 10 minutes prior to drug ingestion ("Minute -10"), and then 30, 60, 90, 120, 180, 240, 300, and 360 minutes after drug ingestion. If at 360 minutes blood pressure is elevated compared to Minute -10, blood pressure will continue to be repeatedly assessed until it has returned to its Minute -10 measurement.

If the Minute -10 assessment (the mean of at least two readings separated by at least 2 minutes) of baseline blood pressure exceeds either 140 systolic or 90 diastolic, periodic blood pressure readings will be obtained (e.g. at 5 minute intervals) to determine if the elevation may be temporary (e.g. due to anticipatory anxiety). If blood pressure decreases to (or below) 140 systolic and 90 diastolic within 20 minutes, capsule administration will proceed. If baseline blood pressure continues to exceed either 140 systolic or 90 diastolic, periodic blood pressure readings will be continued and the study physician will be contacted. The study physician can authorize drug administration if the study physician believes that it is safe to proceed and if the last two blood pressure readings do not exceed 155 systolic or 95 diastolic.

The patient will ingest the psilocybin capsules with about 4 ounces of water and then be instructed to lie down on the couch wearing eyeshades and listening to a preselected music soundtrack via headphones. The subject will be instructed to focus their attention internally and to attempt to interact minimally with the two therapists who will be present in the room throughout the drug session, but will be as non- directive as possible in their interactions with the patient. In the event of a psychologically challenging experience such as significant anxiety or confusion, the therapists will provide verbal reassurance. Patients will have been instructed in the preparatory therapy session to notify the study therapists if during the treatment they feel anxiety or fear.

In the event of a psychiatric emergency, verbal de-escalation and physical and/or chemical restraint will be used to maintain the safety of the subject and the therapists, according to the clinical judgment of the on-call study physician. All possible efforts will be made to avoid using restraints of any kind. Subjects will not be allowed to leave the premises until the drug effects have worn off.

In the event of a medical emergency, subjects will be evaluated by the on-call study physician who will be on-site for all drug administrations. At least one ACLS-certified study clinician will be on-site for all drug administrations. While expected to be rare, the most likely serious adverse event to occur would be a hypertensive crisis. If a subject's blood pressure becomes grossly elevated (SBP >180mmHg, DBP >110mmHG) or unsafe (BP elevations with associated symptoms such as chest pain or shortness of breath), blood pressure will be rechecked immediately in both arms and the on-call physician will be notified if s/he is not already in the treatment room. If the subject is clinically suspected of being in ***hypertensive emergency*** (with signs of end-organ damage), then the subject will be transported to the UCSF Emergency Department for further evaluation and treatment. The Emergency Department's door is less than a 1 minute walk from the Langley Porter Psychiatric Institute. If the patient if determined to be in ***hypertensive urgency*** (without clinical signs of end-organ damage), then blood pressure will be re-assessed with greater frequency while the study physician continues to her/his evaluation for signs of clinical instability, and the study physician may attempt to calm the subject with verbal de-escalation or an anxiolytic (e.g. lorazepam) as transient hypertension is most likely to be due to a challenging psychological experience. If after 20 minutes the hypertensive urgency has not improved, the study physician will evaluate the need for transporting the subject to the Emergency Department for further evaluation and treatment. In the case of ***acute chest pain***, the on-call study physician will have available sublingual nitroglycerin to administer to the subject and an electrocardiogram machine. A crash cart is located in the building, but the goal will be to transport a decompensating patient to the Emergency Department prior to the crash cart becoming imminently necessary. In the event of a suspected ***hypoglycemic episode in a***

6.4.6.1 Focus Group (Week 8)

Two weeks after the last group therapy session, subjects and their caregivers/important others will be invited to participate in a focus group wherein they will be asked to give feedback regarding their experiences in the study. Effort will be made to get both responders and non-responders to attend the focus groups. A clinical rater will administer the C-SSRS(Interval) to each subject. Prior to the focus group each participant will fill out the DS-II and ICG. This will be audio-recorded for subsequent qualitative analysis. See Appendix C for focus group guide.

6.4.6.2 3-Month Follow-up for Subjects

At 3 Months, patients will be emailed a link to the following measures to be completed in REDCap: AMAS, AUDIT, CESD-R, DS-II, DUDIT, DUFSS-5, ECR-M16, HARSI, ICG, MQoL-RS, NR-6, PCL-5, SAHD, SCS-R, STAI, PTGI-SF, IPIP-OE-20, MAIA-R, CTC, and the CSS. They will be called and encouraged to complete the measures. If they have difficulty with email or filling out the forms electronically, paper-and-pen measures will be sent to them with a self-addressed envelope for returning the measures.

6.4.6.3 3-Month Patients for Caregivers/Important Others

At 3 Months, primary caregivers/important others will be emailed a link with the following measures to be completed in REDCap: CORF and CSS. They will be called and encouraged to complete the packet.

6.4.6.4 3-Month Qualitative Interviews

Between the Focus Group and the 3-month follow-up, subjects and caregivers/important others will be invited to participate in a semi-structured interview of their experience in the study. These interviews will be analyzed to detect potential mechanisms of the intervention as well as outcomes not addressed by the study measures. See Appendix C for interview guide.

6.5 Discontinuation of Therapy

The Investigator will withdraw a patient whenever continued participation is no longer in the patient's best interest. Reasons for withdrawing a patient include, but are not limited to, disease progression, the occurrence of an adverse event or a concurrent illness, a patient's request to end participation, a patient's non-compliance or simply significant uncertainty on the part of the Investigator that continued participation is prudent. There may also be administrative reasons to terminate participation, such as concern about a patient's compliance with the prescribed treatment regimen.

6.6 Dietary Restrictions

No dietary restrictions are included in the protocol.

6.7 Prohibited Medications

Patients are prohibited from using medications from the following classes while enrolled in the study:

- Serotonin Reuptake Inhibitors (SSRIs and SNRIs)
- Tricyclic Antidepressants (TCAs)
- Monoamine Oxidase Inhibitors (MAOIs)
- Atypical antidepressants (e.g., mirtazapine, nefazodone, buspar)
- Antipsychotics/Neuroleptics (typical and atypical)
- Anti-epileptics or mood stabilizers (e.g., lithium, valproate)

as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure.

7.3.2.3 Serious

An adverse event or suspected adverse reaction is considered *serious* if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.3.2.4 Life-threatening

An adverse event or suspected adverse reaction is considered *life-threatening* if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.4 Recording of an Adverse Event

All adverse events will be entered into UCSF REDCap, whether or not the event is believed to be associated with use of the study drug. Data about these events and their severity will be recorded using the NIH Division of AIDS Table of Grading of Severity of Adult and Pediatric Adverse Events V2.0.

The Investigator will assign attribution of the possible association of the event with use of the investigational drug, and this information will be entered into UCSF REDCap using the classification system listed below:

Relationship	Attribution	Description
Unrelated to investigational drug/intervention	Unrelated	The AE *is clearly NOT related* to the intervention
	Unlikely	The AE *is doubtfully related* to the intervention
Related to investigational drug/intervention	Possible	The AE *may be related* to the intervention
	Probable	The AE *is likely related* to the intervention
	Definite	The AE *is clearly related* to the intervention

Signs or symptoms reported as adverse events will be graded and recorded by the Investigator. When specific adverse events are not listed in the above NIH DAIDS Table of Grading of Severity, they will be graded by the Investigator as *none*, *mild*, *moderate* or *severe* according to the following grades and definitions:

Grade 0	No AE (or within normal limits)
Grade 1	Mild: Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated
Grade 2	Moderate: Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated
Grade 3	Severe: Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated
Grade 4	Potentially life-threatening: Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death
Grade 5	Death related to AE

7.5 Follow-up of Adverse Events

All adverse events will be followed with appropriate medical management until resolved. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

7.6 Adverse Events Monitoring

All adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into UCSF REDCap, as noted above.

The Investigator will assess all adverse events and determine reportability requirements to the Data and Safety Monitor (DSM) and UCSF's Institutional Review Board, the Committee on Human Research (CHR); and, when the study is conducted under an Investigational New Drug Application (IND), to the Food and Drug Administration (FDA) if it meets the FDA reporting criteria.

In addition, all adverse events and suspected adverse reactions considered "serious," entered into UCSF REDCap will be reviewed and monitored by the Data and Safety Monitor on an

ongoing basis, discussed at DSM meetings which take place after each therapy group completes the 8-week intervention.

7.7 Expedited Reporting

Reporting to the Data and Safety Monitor

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the DSM within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

Reporting to UCSF Committee on Human Research (Institutional Review Board)

The Principal Investigator must report events meeting the UCSF CHR definition of "Unanticipated Problem" (UP) within 10 business days of his/her awareness of the event.

Expedited Reporting to the Food and Drug Administration

If the study is being conducted under an IND, the Sponsor-Investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32).

The Investigator must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor-Investigator needs to ensure that the event meets all three definitions:

- Suspected adverse reaction (as defined in 7.3.2.1)
- Unexpected (as defined in 7.3.2.2)
- Serious (as defined in 7.2.3.3)

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

Reporting to Pharmaceutical Companies providing Study Drug

Serious adverse reactions will be reported to the Heffter Research Institute and the Usona Institute, which are consultants for this study.

8.2.2 Replacement Policy

Study subjects who have been assigned to a group and drop out prior to the first group session can be replaced by a new subject who will be assigned to the same group. Subjects who drop out after the first group therapy session will not be replaced.

8.2.3 Accrual estimates

The annual number of eligible patients is high given the size of the population of HIV-seropositive people in the San Francisco Bay Area. In 2014, San Francisco reported 15,979 people living with HIV, of whom 9,202 were at least 50 years old [8]. If accrual falls short of expectations, advertising and recruitment efforts will be expanded.

8.3 Interim Analyses and Stopping Rules

After the occurrence of one Adverse Event judged to be Severe and potentially related to the drug/intervention, enrollment will be stopped until a Safety Review has been completed and the appropriate protocol amendments implemented.

8.4 Analyses Plans

The study's biostatistician is Matthew Boden, Ph.D. Alongside the PI, Dr. Boden will be co-responsible for assuring that clinical data are correctly collected, stored and analyzed. He will work directly with the PI to assure that interpretations of these data are coherent and justified. Dr. Boden's professional interests are rooted in the research, evaluation and implementation of evidence-based treatments for complex and severe mental disorders. As a Health Science Specialist at the Center for Innovation to Implementation (Ci2i), Veterans Affairs (VA) Palo Alto Health Care System, Dr. Boden investigates the clinical effects and implementation of evidence-based psychosocial treatments for psychotic, anxiety, and substance use disorders. His research utilizes a variety of assessment (e.g., structured clinical interviews, biological assays) and statistical (e.g., linear mixed models, exploratory structural equation modeling) techniques. As a Senior Evaluator at the Program Evaluation and Resource Center (PERC), VA Office of Mental Health Operations (OMHO), Dr. Boden supports OMHO's nationwide program evaluation and quality improvement efforts.

8.4.1 Analysis Population

All patients who enroll in the study will be included in analyses of safety and tolerability.

All patients who make any contact at all with the study (including those who are screened out over the phone) will be included in analyses of feasibility.

All patients who enroll in the trial will be included in analyses of efficacy. Repeated efficacy measures will be gathered and trended, regardless of missing data or protocol non-adherence.

All patients who participate in at least one group therapy session will be included in analyses of psychotherapeutic process.

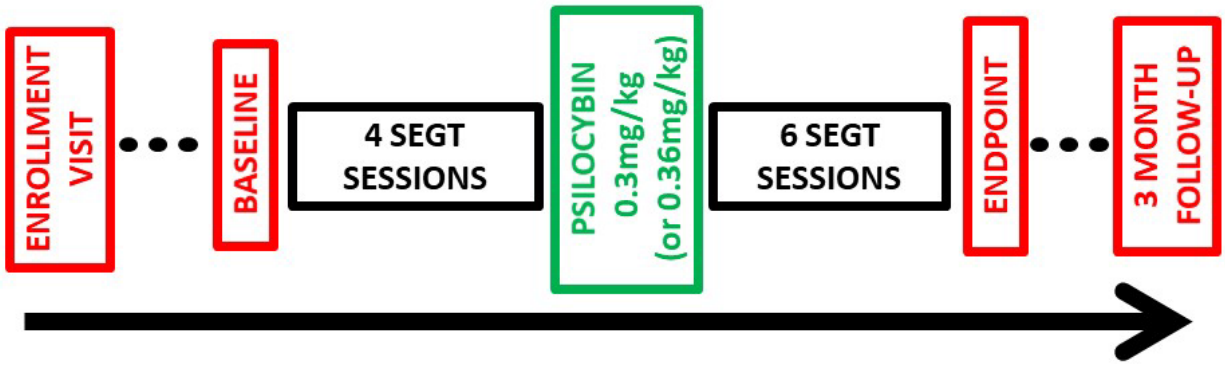
8.5 Primary Analysis

Safety analyses will be performed for all patients who enroll in the study. The study will use the NIH Division of AIDS Table of Grading of Severity of Adult and Pediatric Adverse Events V2.0 to

1 Introduction

We propose to conduct a clinical trial of psilocybin-assisted psychotherapy for demoralization in Long-term AIDS Survivors (LTAS). This will be the first trial of psilocybin-assisted psychotherapy specifically for people living with HIV (PLH) and it will be the first modern trial of psilocybin-assisted *group* psychotherapy for any indication. The study will consist of up to six groups of six gay-identified HIV-seropositive people ≥50 years of age who were diagnosed with HIV prior to the clinical availability of combination antiretroviral therapy (~1996) and who have moderate-to- severe demoralization [13, 27]. Psychotherapy groups may be organized based on gender identity and sexual orientation to create homogenous groups. Each subject will undergo 10 sessions of a modified form of Supportive-Expressive Group Therapy [25] and one individual psilocybin treatment session [24] after group four of the intervention. Quantitative and qualitative measures of psychotherapeutic process will be used to explore the mechanisms by which this novel therapy seems to work, particularly on the interpersonal level. Quantitative and qualitative measures will assess changes in quality of life of the partners/caregivers of subjects undergoing the intervention. This study will contribute to the available data on the safety, feasibility and efficacy of psilocybin-assisted psychotherapy for existential distress in palliative care patients, and importantly will provide the first of such data on a palliative care population other than cancer patients [28].

Fig. 1 INTERVENTION TIMELINE



1.1 Background on Indication

Existential Distress and Demoralization

Existential distress is a form of psychological suffering that occurs when one is confronted with one's own mortality [11]. Demoralization is a form of existential distress that is prevalent in the palliative care setting and is characterized by hopelessness and helplessness due to a loss of purpose and meaning in life [12, 13]. Demoralization is associated with, but distinct from, depression, anxiety, isolation, and the desire for hastened death [29]. In palliative care patients, demoralization has been shown to be more strongly associated with suicidal ideation than depression is [30]. In modern palliative care, the current standard is to address existential and spiritual issues in patients and their family members [31, 32]. Following the lead of innovators like Frankl [33] and Yalom [34], investigators have over the last two decades devised a number of existential psychotherapies [35-40] with varying impact on depression, anxiety and quality of life [26, 41]. Arguably, what these therapies have in common is what Cassel [42] long ago prescribed

- Change in group process will be assessed as the difference in rate of progression of the Hill Interaction Matrix score pre- and post-psilocybin.

- Change in group process will be assessed as the change in the Individual Group Member Interpersonal Process Scale over time.

- Expectancy effects will be estimated based on the pre-psilocybin total score of the Credibility/Expectancy Questionnaire.

- Subjective experience of a psilocybin treatment session will be evaluated with the Mystical Experience Questionnaire—30 and the Challenging Experience Questionnaire.

- Change in attachment security will be defined as the difference in pre-treatment, post-treatment, and 3-month follow-up mean scores of the Experiences in Close Relationships scale—Modified 16.

- Qualitative analysis of therapy session video footage, semi-structured patient interviews, focus groups and process notes written by study staff.

- Change in inclusion of other in self will be defined by the difference in pre-treatment, post-treatment, and 3-month follow-up results of the Inclusion of Other in Self measure.

until death, whichever occurs first. Patients removed from study for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment related adverse events.

3.6 Randomization Procedures

Patients will not be randomized; this is an open-label pilot trial with one treatment arm.

3.7 Study Timeline

3.7.1 Primary Completion

The study will reach primary completion 36 months from the time the study opens to accrual.

3.7.2 Study Completion

The study will reach study completion 48 months from the time the study opens to accrual.

lifetime.[174]

McGill Quality of Life Questionnaire-Revised-Short (MQoL-RS)—A well-validated 15-item 11-point Likert scale that assess quality of life in palliative care patients by assessing the following domains: Overall quality of life, Physical well-being, Psychological well-being, Social support and Existential well-being. We will only use 4 items, which are Parts A (Overall quality of life) and B (Physical symptoms).

Multidimensional Assessment of Interoceptive Awareness-Revised (MAIA-R)—A well-validated 32-item 6-point Likert scale of bodily and mental awareness that measures the following 8 domains: Noticing, Not-distracting, Not-worrying, Attention regulation, Emotional awareness, Self-regulation, Body listening and Trusting [175]. If this study, we will use the Emotional awareness (5-tiems), Self-regulation (4-items) and Trusting (3-items) subscales.

Mystical Experience Questionnaire-30 (MEQ-30)—A well-validated 30-item 6-point Likert scale ("none; not at all" to "extreme [more than any other time in my life]") self-report measure of mystical-type experiences [127], derived from the earlier work of Pahnke et al. [122].

Nature Relatedness Scale, Short-Form Version (NR-6)—A 6-item version of a well-validated 5-point Likert scale self-report measure of environmental connectedness [176].

Palliative Performance Scale version 2 (PPSv2)—A validated clinician-administered tool based on the Karnovsky Performance Scale but adapted for a palliative care population [117, 177].

Persisting Effects Questionnaire—Spirituality (PEQ-S)—An instrument developed by Griffiths et al for subjects who have been administered psilocybin to assess enduring changes in attitudes about life, attitudes about self, mood changes, relationships, behavioral changes, and spirituality [141]. The measure also includes 4 questions about the drug experience itself concerning personal meaningfulness, spiritual significance, how psychologically challenging it was, and personal psychological insights gained. We will only use the Spirituality subscale (59-item, 6 point Likert scale ["none; not at all" to "extreme"]), and the four questions about the psilocybin experience.

Post-traumatic Growth Inventory-Short Form (PTGI-SF)—A validated 10-item 6-point Likert scale meant to assess the following psychological factors in populations that have suffered a traumatic event or major crisis: quality of relationships with others, openness to new possibilities, personal strengths, spiritual change, and appreciation of life [178].

PTSD Checklist (PCL-5): A validated 20-item, 5-point Likert scale (from "Not at All" to "Extremely") to measure symptom criteria for PTSD from the DSM-5. [179]

Schedule of Attitudes towards Hastened Death (SAHD)—A 20-item True/False self- report measure of the desire for hastened death validated in patients with HIV/AIDS and other palliative care conditions [180].

Social Connectedness Scale-Revised (SCS-R)—A well-validated 8-item 6-point Likert scale (negatively-worded items rated from "strongly agree" to "strongly disagree") self-report measure which has shown strong construct, convergent and discriminant validity as well as reliability ($\alpha >$ .92) for assessing the degree to which subjects feel connected to their social environment [181]

State-Trait Anxiety Inventory (STAI)—A 40-item 4-point Likert scale that is the gold standard in self-report measures for state and trait anxiety [182, 183].

Supportive-Expressive Group Therapy Topic Grid (SEGT-TG)—A measure developed by Spiegel and Spira for the original studies of SEGT [75]. Independent raters watch video of

subject with diabetes mellitus, a finger stick blood glucose will be checked on an as needed basis, and fruit or oral glucose tablets will be available.

As the drug effects begin to wear off at the 5-6 hour mark, the therapists will engage the patient in a therapeutic interview to explore the experience (see Appendix C for interview guide); this discussion will also be videotaped. A clinical rater will administer the C-SSRS(Interval). Only once patients are deemed to be free of the acute effects of the drug, and after at least 7 hours have passed since ingestion of the drug, will the participant be allowed to leave the premise in the company of a caregiver who has been instructed on how best to support the patient over the coming days.

The patient and caregiver will be given a study clinician's pager or work cell phone number in case of any clinical event off-site that needs further assessment. Patients must agree not to drive themselves home, nor to drive later that same day after they arrive home. Patients will be instructed to write a detailed account of their experience during the drug session at some point over the next week.

In the event that a participant did not arrange a friend/family member to accompany them home, the participant will be required to stay with the study clinicians longer, will be encouraged to eat, and then the participant will be escorted to the curb by study staff and seen into a taxi/Lyft/Uber that will be instructed to take them home. The participant will also be instructed to call the study MD when they arrive home. All efforts will be made to avoid this situation. In the weeks prior to the medication session, participants will be regularly reminded to arrange for someone to accompany them home.

The following day patients will return to the study site to meet with a study therapist and engage in a therapeutic discussion of their experience for 90 minutes. Before the session patients will present to the Clinical Research Service for a blood draw for these studies: CBC, CMP, CRP. Patients will complete the MEQ-30, ChEQ, STAI, SAHD, MQoL, and the C-SSRS(Interval) at this visit. Patients may again meet with study staff in person prior to the next group therapy session if they request this or if study clinicians deem it clinically warranted.

6.4.4.3 Group Therapy Sessions #5-10 (Weeks 4-6)

Patients will undergo six group therapy sessions each 90-minutes long. Video footage of a random sampling of sessions will be analyzed with the HIM, SEGT-TG, IGMIPS and the GPIRS. Prior to each session, patients will be screened for adverse events and evaluated with the CSSR-S. Prior to sessions 5, 7 and 9, participants will fill out the CTC. After sessions 6, 8 and 10, participants will fill out the GQ. At the end of session 5, participants will fill out these questionnaires: CESD-R, DS-II, ICG, PCL-5, HARSI. After session 7 participants will fill out the DS-II and ICG.

6.4.5 Endpoint Assessments

6.4.5.1 Endpoint (Week 6) Study Measures for Subjects

Immediately after the last group therapy session (Week 8), patients will complete the AMAS, CESD-R, DS-II, DUFSS-5, ECR-M16, ICG, MQoL-RS, NR-6, PCL-5 SAHD, SCS-R, STAI, PTGI-SF, IPIP-OE-20, MAIA-R, HARSI, CTC, and CSS. A clinical rater will perform a MoCA and CGI for each subject.

6.4.5.2 Endpoint (Week 6) Study Measures for Caregivers/Important Others

Patients' primary caregivers/important others will complete the CORF and CSS.

6.4.6 Post-treatment/Follow Up Assessments

- Efavirenz (Sustiva, in Atripla)
- OTC supplements intended to affect mood or anxiety (e.g., 5HT-P or St. John's Wort).

Conditional medication restrictions

- Trazodone
  - Trazodone ≤50mg/24hr for insomnia is allowed, but not within 48hr of psilocybin session
- Benzodiazepines
  - PRNs are not allowed 24hr prior to the psilocybin session
  - "z-drugs" (e.g., zolpidem) are not allowed 24hr prior to the psilocybin session

Individuals who at screening would be excluded for taking contraindicated antidepressants, anxiolytics, stimulants or herbal supplements can be considered for the study if—under the guidance of their usual physician—they successfully taper off these medications and demonstrate a period of psychiatric stability lasting at least 2 weeks. One exception to the required 2-week period is for individuals taking low dose TCAs (≤50mg imipramine equivalent) for reasons other than depression or anxiety (e.g., peripheral neuropathy or insomnia). These individuals may, under the guidance of their usual physician, taper off these medications and then be enrolled in the study once they are no longer taking the TCA.

6.8 Study Clinicians

Study clinicians (group therapists and treatment session guides) will be approved by a panel consisting of: Dr. Josh Woolley (PI), Dr. Alicia Danforth (UCLA psilocybin team, and lead clinical supervisor for UCSF the team), Dr. Brian Anderson (UCSF psilocybin team), and Robert Jesse (Johns Hopkins psilocybin team). Group therapists and treatment session guides will all be licensed clinicians (MD, RN, NP, MFT, LCSW, PhD, PsyD, Chaplain, etc) in the state of California; an exception will be made if the person is unlicensed but currently enrolled in a clinical training program and has had sufficient clinical exposure, according to the judgment of the above-mentioned panel. The selection of therapists/guides will give preference to those who have: 1) prior clinical experience working with the study population; 2) have demographic similarities to the study population (age, gender, sexual orientation); 3) prior experience conducting group therapy; 4) prior experience working with individuals under the influence of psychedelics either in research settings or harm-reduction settings (such as the Zendo Project); 5) have completed the CIIS certificate program in Psychedelic-assisted Psychotherapy and research.

Group therapist pairs will consist of one lead and one secondary therapist. The lead must have had significant experience as a group therapy leader; the secondary must have some experience as a group therapy leader. Group therapists will undergo at least 16 hours of training in Supportive-Expressive Group Therapy (SEGT) by studying SEGT training videos, the SEGT adherence rating scales that will be used in the study, and the 3 following SEGT manuals: the original manual for metastatic breast cancer patients [75], the manual for brief SEGT in newly diagnosed breast cancer patients [76], and the adaptation by Maldonado et al for patients with AIDS [78]. All group therapists will undergo at least one 'dry run' session of the SEGT method prior to starting a group.

Each subject will have 2 guides working with them in their drug treatment day (not necessarily one male and one female). At least one of the treatment session guides will be one of the subject's group therapy co-therapists. Treatment session guides will undergo instruction by Dr. Alicia Danforth and/or Dr. Anderson. Overall clinical supervision will be a responsibility shared by Dr. Josh Woolley (Co-PI), Dr. Brian Anderson (PI) and Dr. Danforth (lead psychotherapy supervisor). Clinical consultation will be available from others involved in the study, such as Dr. Jim Dilley, Co-Investigator of this study and founder and of the UCSF Alliance Health Project, as well as Dr. Rob Daroff, a study clinician who is a staff psychiatrist at the SFVA with many years experiencing running psychotherapy groups for gay men in San Francisco.

8 Statistical Considerations and Evaluation of Results

8.1 Study Design

This open-label single-arm mixed-methods pilot study will use descriptive statistics and qualitative methods to evaluate safety and feasibility in terms of rates of adverse events, patient recruitment and retention, and feedback on the intervention's utility, content and duration. Given the small sample size of this study, small-to-medium effect sizes will likely be undetectable; and so descriptive statistics will be used to report changes in mean measures at baseline compared to the endpoint, and again at the 3-month follow-up. Exploratory ANOVAs will also be done to model changes in therapeutic process values (e.g., group cohesion) over time. Qualitative thematic analysis will also be used to evaluate verbal and written reports of patient and caregiver/important other experiences with the study in order to optimize implementation of the intervention in larger, future trials.

8.1.1 Randomization

No randomization procedures will be used.

8.1.2 Stratification Factors

No stratification procedures will be used.

8.2 Determination of Sample Size and Accrual Rate

8.2.1 Sample Size and Power Estimate

This pilot study of the safety and feasibility of psilocybin-assisted group therapy aims to enroll at least 18 subjects, and will have a maximum total sample size of 36. We estimate needing to enroll 18 subjects given attrition rates of up to 45% reported in trials of other group therapies for existential distress in palliative care patients [118]. For comparison, four different safety and feasibility pilot studies of psilocybin-assisted psychotherapy have been conducted over the last two decades, and have included 9, 10, 12 and 15 patients each [18, 111, 112, 114]. Four recently published feasibility pilot studies of meaning-focused group psychotherapies for palliative care patients have included 5, 11, 11, and 16 patients each [40, 185-187].

Group therapy studies should include at least 2 groups of at least 4-6 members [138], so we plan to have at least 8 subjects complete the intervention. We expect to be able to enroll at least 6 subjects every 6 months.

Because the proposed study is a pilot focused on investigating safety and feasibility, power calculations for efficacy measures are not indicated. Pilot studies are often used to estimate values that are then utilized in power calculations for full-scale trials. Indeed, we will estimate effect size (ES) and the intraclass correlation coefficient (ICC) [135] for the intervention based on our preliminary efficacy results. Group psychotherapy trials generally require large sample sizes to demonstrate statistical significance in change in efficacy measures given the likely interdependence of clinical outcomes when interventions are delivered in groups [135, 136]. Thus, future full-scale trials can utilize our estimates to derive adequate, and likely large, sample sizes.

classify adverse events. Descriptive statistics (percentages) will be reported for the incidence of any Adverse Events reported, including suicidality as measured by the C-SSRS. Median scores will also be calculated for total scores of the feasibility measures: CSS, CrEQ, and PEQ-S. The differences of mean pre- and post-treatment scores on the CORF will be calculated. Differences in individual pre- and post-treatment MoCA scores will be assessed for each individual. Therapist protocol adherence will be reported as a rate of discussion topic deviations from the protocol.

8.5.1 Exploratory Analyses

Change in efficacy measures from pre-treatment to post-treatment to 3-month follow-up will be analyzed with descriptive statistics to represent trends in mean levels. Recognizing that the calculations will likely be underpowered, we will also perform ANOVAs of the secondary outcome measures. To assist in gauging the clinical relevance of these data relative to measurement error, and to overcome some of the limitations of the study's small sample size, Reliable Change Indices (RCI) will be calculated [188]. Data from efficacy measures will also be used to estimate effect sizes and intraclass correlation coefficients for use in larger, future studies.

Change in process measures (e.g., the HIM, QPIRS and GQ) over time will be analyzed with ANOVAs to assess the slopes of individual participants and of the whole sample.

Qualitative thematic analyses will be conducted according to the methods outlined in Section 6.3. Iterative inductive analyses will be performed with the aid of NVivo analytical software.

8.6 Study Results

Study results will be reported following the guidelines of the TREND Statement for reporting of results from non-randomized interventions [189]. The study biostatistician will oversee or review the interpretation of all the above analyses and descriptive statistics.