Abbreviated Title: CALM Therapy

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Title: Managing Cancer and Living Meaningfully (CALM) Therapy in Individuals Diagnosed with a Primary Central Nervous System Tumor

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Behavioral Intervention: CALM

PRÉCIS

Background:

- Psychological distress is an emotional state experienced by primary central nervous system tumor (PCNST) patients throughout the illness trajectory. It can often be under-identified in this patient population.
- Limited therapeutic interventions in managing distress symptoms can allow symptoms to linger without tailored mechanisms to manage the emotional challenges experienced with a tumor diagnosis. Individualized therapy in advanced cancer patients is a preferred method over pharmacological interventions when managing psychological distress, but more evidence-based research is needed to address the benefits.
- The CALM intervention is a brief, individualized psychotherapeutic intervention established to meet an unmet need to address psychological distress and promote well-being in advanced cancer patients. Previous studies implementing the CALM intervention have focused on metastatic and advanced cancer patients and have reported positive effects. Implementing the CALM intervention in a sample of PCNST patients will be one of the first studies to identify the preliminary effectiveness.

Objective:

- To demonstrate the effects of the CALM intervention in the reduction of depressive symptoms using the PROMIS-Depression scale in PCNST participants, from baseline to 6 months.

Eligibility:

- Adult participants ≥ 18 years of age with a PCNST diagnosis who are undergoing standard of care or experimental treatment.
- The ability of the subject to speak English.
- Subjects who have a life expectancy of at least 3 months from time of study entry to allow for participation in the 3 required sessions.
- The ability of the subject to understand and willing to sign a written informed consent document as determined by the assessment of the clinical team.

Design:

- A total of 100 participants may be enrolled
- Neuro-Oncology participants being seen in the clinical center or receiving telehealth services will be screened to participate. Participants will be assigned a CALM therapist and all sessions will be completed remotely.
- Data from standardized measures will be collected at 3 timepoints (baseline, 3 months, and 6 months) and qualitative interviews will be completed after the 3rd CALM session for a select number of participants until data saturation is reached (estimated to be 15-30).
- The approximate time for CALM therapy sessions is 45-60 minutes.

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STATEMENT OF COMPLIANCE

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

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

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

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

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

- To demonstrate the effects of the CALM intervention in the reduction of depressive symptoms using the PROMIS-Depression scale in PCNST participants, from baseline to 6 months.

1.1.2 Secondary Objectives

- To demonstrate the short-term effects of the CALM intervention in the reduction of depressive symptoms using the PROMIS-Depression scale in PCNST participants from baseline to 3 months.
- To determine the effects of the CALM intervention on death anxiety using the Death and Dying Distress Scale at both 3 and 6 months, compared to baseline.
- To describe the feasibility of implementing CALM remotely in a PCNST population, including eligibility, accrual, compliance, adverse effects, study completion, and participant satisfaction with the intervention.

1.1.3 Exploratory Objectives

- To determine the effects of the CALM intervention on psychological well-being as measured by the Quality of Life Cancer scale (QUAL-EC) and the modified and brief Experiences in Close Relationships (ECR-M-16) questionnaire at both 3 and 6 months, compared to baseline
- To explore the effects of the CALM intervention, more specifically the relationship between distress and symptom burden as measured by the M.D. Anderson Symptom Inventory-Brain tumor (MDASI-BT) for those with brain or brain and spine tumors and the M.D. Anderson Symptom Inventory-Spine Tumor (MDASI-SP) for those with spine tumors, symptom severity and symptom factor scores.
- To explore the effects of the CALM intervention on the relationship between distress and symptom interference as measured by the MDASI-BT or MDASI-SP interference scores.
- To explore the effects of the CALM intervention on health status as measured by the EQ-5D.

1.2 BACKGROUND AND RATIONALE

1.2.1 Psychological distress

Psychological distress is estimated to affect between 30% and 73% of patients with primary malignant brain tumors (1, 2) (3). Limited data exists in the primary spine tumor patient population, but a recent unpublished analysis of data collected as part of the NOB-Natural History Study on 73 patients revealed that 38% reported moderate-severe distress on the M.D. Anderson Symptom Inventory-Spine Tumor (MDASI-SP), and 23% moderate-severe anxiety and 14% moderate-severe depression using PROMIS self-report instruments. Distress is usually under-identified in brain tumor patients (4) (5) and has been found to persist across the illness trajectory (6). Mood disturbance in glioma patients has been found to be similar to breast cancer populations (7). Several

research findings have reported the associations between emotional distress with performance status and psychotropic medication use (8) (9), emotional distress in survivorship (8), symptom burden in minority CNS patients (10), sleep disturbance effects on mood interference (11), increased mood disturbance association with low hope (12), confirming the distress glioma patients experience. The majority of studies in PCNST patients has been cross-sectional or retrospective in nature (13-15), but indicate that depressive symptoms commonly occur in approximately a third of patients. The few longitudinal studies that have been done, indicate that patients remain with symptoms through the follow-up period (3 and 6-month time point)(14, 15).

As the first stage in a research program dedicated to understanding and treating psychological distress in patients with advanced cancer, a Canadian Institutes for Health Research (CIHR)-funded longitudinal, mixed-methods study of patients with metastatic gastrointestinal (GI) and lung cancer, with an expected survival of 12-18 months was completed at Princess Margaret Cancer Centre (PM) (16). Authors identified the prevalence, course, and predictors of depression and demoralization, showing that clinically significant depressive symptoms were present in 27% of the baseline sample (16). Based on cross-sectional and longitudinal evidence, the authors proposed that these symptoms are best understood as a final common 'pathway of distress', emerging in response to the interaction of multiple disease-related, individual and psychosocial factors (16-21). The most prominent of these is the physical burden of disease, attachment anxiety (i.e. worry about the availability of supportive relationships and the capacity to make use of them for emotional support), lower self-esteem, hopelessness, and impaired spiritual well-being (16, 19).

Depressive symptoms in cancer patients deserve attention because they are associated with psychological well-being and quality of life (22), noncompliance with medical treatment (23), distress in caregivers (20), and increased health care utilization (24). Unfortunately, depression is often undetected and untreated in cancer and other medical populations (25, 26). Researchers at PM have shown that the majority of patients with metastatic cancer and clinically significant depressive symptoms are not referred for psychosocial care and that most of those referred do not receive specific or adequate treatment for depression (27). Importantly, findings in patients with advanced cancer suggest that psychological treatments for depression are preferred over pharmacological ones (28, 29). Although group therapy has received considerable attention in the literature (30-33), individual psychotherapy is often preferred by patients with advanced disease and is often more feasible to deliver because sessions can be flexibly tailored to patients' individual needs, taking into account other clinic appointments and fluctuations in health status (34-37).

To address the lack of evidence-based, individual therapies tailored for this population with advanced disease who are earlier in the disease trajectory, the clinical and research team at PM developed a brief, individual psychotherapeutic intervention to alleviate depression and promote psychological well-being. This psychotherapy, designated **CALM** (Managing **C**ancer **A**nd **L**iving **M**eaningfully) (38), was designed to address the specific problems and risk factors that contribute to the emergence of depressive symptoms in this circumstance (16, 19). CALM provides support and reflective space for the processing of thoughts and emotions evoked by this traumatic condition and facilitates the resolution of practical and existential questions that face individuals with metastatic disease.

1.2.2 CALM Psychotherapy

CALM is a semi-structured, manualized, individual psychotherapy designed for patients with advanced cancer and their loved ones. It shares features with manualized supportive-expressive (30, 39-43), cognitive-existential (44, 45), and meaning-centered (46) group psychotherapies applied to patients with advanced and terminal disease. It was developed based on empirical data, clinical observations, and the theoretical foundations of relational (47), attachment (48), and existential (49) theory. It is informed by Princess Margaret's team CIHR-funded longitudinal research aimed at identifying the antecedents and course of psychosocial morbidity in individuals with metastatic cancer (16-19, 21, 50).

CALM includes 3-6 individual therapy sessions, each approximately 45-60 minutes in length, delivered over 3-6 months. Additional sessions may be offered if clinically indicated while the participant is on the study, with the CALM domains being revisited if the participant is still experiencing challenges and the CALM therapist identifies this need to help the participant process any additional feelings. A maximum of 3 booster sessions will be offered. The sessions cover 4 domains: 1) symptom management and communication with health care providers; 2) changes in self and relations with close others; 3) sense of meaning and purpose, and 4) the future and mortality (38). CALM will be done following the manual that was created by the researchers at Princess Margaret (PM), which is currently in print (51). All modules will be addressed with each patient, but the sequencing and time devoted to each domain will vary, based on the concerns that are most relevant to each patient. The patient's caregiver (e.g., spouse, adult son/daughter, family member), or other persons accompanying the patient are encouraged to participate in one or more of the therapy sessions, as deemed appropriate by the patient and therapist. CALM can be delivered by specially trained therapists from a wide range of disciplines, including social work, nursing, psychiatry, psychology, and medicine (38, 52).

Research conducted over the past decade has shown that CALM is a feasible, acceptable, and effective therapy for patients with advanced or metastatic cancer. In qualitative interviews conducted during the pilot phases of CALM, participants reported that "[CALM] allowed me to express my fears while maintaining my dignity," "gave me a place to talk openly without having to be positive all the time," "[allowed me to be] seen as a whole person within the medical system," diminished fears of taking necessary pain medication or accepting help from others, and "[caused me to be] less afraid of dying." There was no negative feedback from participants about their experiences of CALM and no withdrawals from treatment based on dissatisfaction with it (53). Additionally, within the feasibility study, patients who completed at least 3 sessions, even with the small sample size and significant attrition, PM researchers found depression and death anxiety, even though small were found to significantly decline over time (54). The randomized controlled trial (RCT) showed that when comparing patients that received the CALM intervention to the Usual Care group, CALM patients reported less severe depressive symptoms at the primary endpoint (3-month), this effect was also greater at the 6-month assessment (55).

This will be one of the first studies utilizing CALM as a telepsychology intervention in a sample of PCNST patients. Common barriers for patients in receiving mental health treatment can include stigma concerns, geographical isolation, time commitments, and transportation. Thus, having the ability to access telepsychology can decrease patient challenges by allowing them the flexibility to be treated in the comfort of one's home, while also optimizing the patient and providers time (56). A recent meta-analysis conducted for depression found no evidence to suggest that the use of synchronous (real-time visual and auditory interactions between patients and

providers) telepsychology was less effective compared to non-telepsychology methods in reducing symptoms (57).

Understanding the effects of CALM using telepsychology in this patient population will help in identifying feasible methods in treating patients' distress and will be used to calculate sample size and effect for a multicenter randomized study, evaluating CALM versus standard of care in the PCNST patient population. This can allow for more tailored psychosocial interventions focused on patients' needs and can provide additional coping mechanisms utilized throughout the illness trajectory in dealing with challenges associated with a PCNST diagnosis.

1.2.3 Questionnaires and Interviews

1.2.3.1 The Patient-Reported Outcomes Measurement Information System (PROMIS)

The PROMIS®-Depression Short Form (version 8a) will be utilized to measure participants' depressive symptoms. This eight-item assessment allows participants to self-report the frequency of depressive symptoms experienced within the past 7 days. Participants are asked to rank symptoms on a scale that includes "never, rarely, sometimes, often and always." PROMIS® has been developed by the U. S. Department of Health and Human Services and is available at no cost (58).

1.2.3.2 The Death and Dying Distress Scale (DADDS)

A validated 15-item scale measuring death anxiety in advanced cancer patients (59) (60). It addresses fears about the dying process and distress about lost opportunities and self-perceived burden placed on others as a result of impending mortality. Scores range from 0-75, higher scores represent greater distress.

1.2.3.3 The modified version of the Clinical Evaluation Questionnaire (CEQ)

This will be used to evaluate the extent to which participants felt supported by their CALM therapist. For this study, 8 items were added to the measure to better capture the extent to which CALM therapy helps participants cope with the future, discuss important things with loved ones, and increase double awareness.

1.2.3.4 CALM Qualitative Interview

A brief, 5-item semi-structured interview was developed by the CALM researchers. Study participants who have completed at least 3 sessions during the course of the study may be asked to complete a qualitative interview. Qualitative interviews will be conducted until thematic saturation is reached (i.e., adequate data has been identified and no new information is expected). Determination of sample size to reach thematic saturation is estimated to be between 15-30 participants (61) (62) (63). The purpose of the interviews is to evaluate participants' overall experience with CALM therapy across each of the four CALM dimensions, the therapeutic alliance, and the structure and timeframe of CALM.

1.2.3.5 The Quality of Life-Cancer Scale (QUAL-EC)

This is a 17-item measure of the quality of life in patient populations near the end of life and includes 4 subscales: Symptom Impact (i.e. list of physical symptoms experienced in the previous month and their frequency, severity, and interference), Preparation for the End-of-Life (i.e., extent to which the family is prepared, financial plans have been made), Relationship with Healthcare Providers (i.e., extent to which patients feel informed, are able to participate in decisions about

their care) and sense of Life Completion (i.e., being able to share important things and to feel connected to others).

1.2.3.6 The modified and brief Experiences in Close Relationships (ECR-M-16)

Attachment insecurities will be assessed using a widely used 16-item measure of attachment security, or the ability to rely on close others for support when distressed, which has demonstrated reliability and validity. It provides subscale scores assessing attachment anxiety (i.e., fear of abandonment) and avoidance (i.e., defensive independence).

1.2.3.7 MDASI-BT or MDASI-SP

This study will use the M.D. Anderson Symptom Inventory-Brain Tumor Module or Spine Tumor Module (MDASI-BT and MDASI-SP, respectively) The MDASI-BT and MDASI-SP have demonstrated reliability and validity in the adult primary brain and spine tumor patient population. This tool represents a modification of the widely used and validated M.D. Anderson Symptom Inventory, with particular attention to symptoms common in patients with brain and spine tumors respectively.

The scales include symptoms rated on an 11-point scale (0 to 10) to indicate the presence and severity of the symptom, with 0 being "not present" and 10 being "as bad as you can imagine." Each symptom is rated at its worst in the last 24 hours. Symptoms included on the instrument include those commonly associated with cancer therapies, common across cancers and focal neurologic symptoms common in those with either brain or spine tumors. The scales both also includes ratings of how much symptoms interfered with different aspects of a patient's life in the last 24 hours. These interference items include general activity, mood, work (includes both works outside the home and housework), relations with other people, walking, and enjoyment of life. The interference items are also measured on 0 - 10 scales. The average time to complete either scale is 5 minutes. Both have demonstrated measures of reliability and validity (64, 65).

1.2.3.8 EQ-5D

EQ-5D™ is a standardized instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, the EQ-5D health questionnaire provides a simple descriptive profile and a single index value for health status. This EQ-5D was developed based on the health status of the community, which are more mobile and have fewer symptoms than the primary central nervous system tumor population.

1.2.3.9 Was It Worth It (WIWI)

The WIWI is a brief questionnaire that is designed to measure a participant's opinion of their participation. WIWI questions are dichotomous (yes/no) and are tailored to be specific to the intervention involved in the study. For the purposes of this study, there will be four yes/no questions that ascertain the participants' satisfaction with the CALM intervention.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

- Subjects with histological or imaging confirmation of PCNST who are undergoing standard of care or experimental treatment.
- Adults (≥ 18 years of age) who are English-speaking
- Subjects who have a life expectancy of at least 3 months from time of study entry to allow for participation in the 3 required sessions.
- Subjects must be enrolled on the Neuro-Oncology Branch Natural History Study 16C0151**.**
- The ability of the subject to understand and the willingness to sign a written informed consent document as determined by the assessment of the treating physicians.

2.1.2 Exclusion Criteria

- Participants without access to a smartphone, computer, or tablet to complete remote sessions.

2.1.3 Recruitment Strategies

Participants will be recruited from the Natural History Study (NHS) # 16C0151 by invitation. This protocol may be abstracted into a plain language announcement that will be posted on NIH websites and on NIH social media platforms. Any recruitment materials will be submitted to the IRB for review prior to implementation.

2.2 SCREENING EVALUATION

2.2.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects.
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes.
- Confirmation of enrollment into NCI protocol “Natural History Study (NCI CC# 16C0151).

2.2.2 Screening activities performed after consent for screening has been signed

No additional screening activities are required.

2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant

Registration & Status Updates found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

2.3.1 Treatment Assignment Procedures

Cohorts

Number	Name	Description
1	Cohort 1	Participants diagnosed with a primary central nervous system tumor who are undergoing standard of care or experimental treatment.

Arms

Number	Name	Description
1	CALM intervention (remote)	All sessions and patient outcome questionnaires will be completed remotely.

Participants in Cohort 1 will be directly assigned to Arm 1.

2.4 BASELINE EVALUATION

Baseline evaluation will be completed within 14 days prior to CALM therapy initiation unless specified otherwise.

Participants will be asked to complete 6 questionnaires at baseline:

1. PROMIS-Depression,
2. Quality of life (QUAL-EC),
3. Death anxiety (DADDS),
4. Attachment Insecurities (ECR-M-16),
5. Presence and severity of the symptoms (MDASI-BT or MDASI-SP) (within 2 months prior to CALM therapy),
6. Health outcomes (EQ-5D) (within 2 months prior to CALM therapy).

For more details, please, see Section **3.2**

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This protocol is a single-arm design and will implement CALM therapy in PCNST patients currently enrolled in the NIH trial 16C0151. Study enrollment, treatment, and all study procedures will be done remotely. Only ISSO approved telehealth platforms will be utilized for telehealth procedures.

All telehealth/remote procedures used in this protocol will be consistent with applicable NIH policies (e.g., Medical Administrative Series policy, M20-1 found at: https://cc-internal2.cc.nih.gov/policies/PDF/M20-1.pdf).

Because our outcome measures (depression, distress, quality of life) are affected by recurrence, we will try to enroll an adequate representation of participants with recurrence and no recurrence.

Participants will be assigned to a CALM therapist and complete baseline questionnaires before starting CALM therapy. Prior to the completion of each session, future sessions will be scheduled with the participant.

CALM includes 3-6 individual therapy sessions, each approximately 45-60 minutes in length, delivered over 6 months. Additional sessions may be offered if clinically indicated while the participant is on the study, with the CALM domains being revisited if the participant is still experiencing challenges and the CALM therapist identifies this need to help the participant process any additional feelings. A maximum of 3 booster sessions will be offered. These additional sessions may be offered if clinically indicated while the participant is on the study.

Prior to each session, CALM therapist will confirm that participant is at home address on file and will have the contact information for a patient identified contact (either living in the home or primary contact outside of the home) and local provider. If the participant is showing signs of being in danger to themselves or others, the participant's location will be confirmed, the patients contact (living in the home or outside) will be contacted by phone and a brief safety plan (identify coping strategies, provide professional emergency contacts) will be created to minimize risk of harm. The CALM therapist will stay in contact with the participant until identified contact or healthcare provider has been reached and they can continue on with management of the participant's care. The information collected from the participant (location, if identified contact is in the home or not) will be provided to the health care provider identified by the participant.

All sessions will be audio-recorded. Sessions will be recorded for treatment integrity and quality assurance, with therapists getting supervision from Dr. Gary Rodin (also an investigator on this study) from Princess Margaret (recordings will be reviewed on a select number of recordings), it will be a way to make sure the CALM intervention is being conducted effectively, that the domains are being targeted and therapists can be evaluated to assess their abilities and improve any areas in the therapeutic relationship. Participants can request that there session not be recorded, and they will still be able to participate in the study. If information is shared during the sessions that the study participant needs continued psychological interventions, the participant's healthcare team will be notified so that appropriate referrals can be made.

CALM includes 4 interrelated domains that will be covered during sessions.

- Symptom management and communication with health care providers
- Changes in self and relations with close others
- Sense of meaning and purpose
- The future and mortality

All modules will be addressed with each participant, but the sequencing and time devoted to each domain will vary, based on the concerns that are most relevant to each participant.

Therapists involved in this study will be health care professionals involved in the care of primary central nervous system tumor participants and able to deliver psychotherapy. CALM therapists are deemed competent in delivering CALM after attending a minimum of one CALM training workshop and following successful completion of 2 training cases (e.g., completion of 3-6 sessions per participant, under supervision), whereby the therapist-in-training sufficiently demonstrates competence in CALM, as judged by the intervention developers or other certified CALM trainers. Supervision from the PM staff will require use of 2 questionnaires.

- The CALM: Evaluation of Therapists Competencies instruments will be used to evaluate CALM therapists to identify adherence to the CALM intervention and to further develop therapist skills during supervision. Both documents will be used by the PM team when supervising the NOB CALM therapists.

Participants will be asked to complete additional questionnaires approximately at 3 and 6 months.

Family caregivers (e.g., spouse, adult son/daughter, family member, or other persons accompanying the participant) of participants involved in the study may be invited to participate in at least one CALM session with the participant. However, caregivers are not required to participate.

Qualitative interviews will be conducted on select participants after their 3rd session to evaluate how participants experienced or evaluated (a) the overall CALM therapy; (b) each of the four CALM dimensions; (c) the therapeutic alliance, and (d) the structure and timeframe of CALM. Caregivers may be invited to complete a qualitative interview with the participant. However, caregivers are not required to participate.

Once participants have completed their therapy sessions and finished their last set of questionnaires, they will be taken off study (see Off-Study Criteria Section **3.6**).

3.2 OUTCOMES QUESTIONNAIRES

Outcome measures will be completed by participants at time points indicated in Study Calendar **3.4** to coincide with CALM intervention session time points and take approximately 40-60 minutes to complete.

These instruments are described in Section **1.2.3**, submitted as a separate document, and will include the following:

- The Patient-Reported Outcomes Measurement Information System (PROMIS-Depression)
- The Death and Dying Distress Scale (DADDS)
- The Quality of Life-Cancer Scale (QUAL-EC)
- The modified and brief Experiences in Close Relationships (ECR-M-16)
- Presence and severity of the symptoms (MDASI-BT or MDASI-SP)
- Health outcomes (EQ-5D)
- The Clinical Evaluation Questionnaire (CEQ)*

- The Was it Worth it Questionnaire (WIWI)*

  ***NOTE**: All Outcomes questionnaires will be completed at baseline, 3-month, and 6-month timepoints, except for the CEQ and WIWI which will be completed at the 3-month timepoint and if more than 3 sessions are completed, the CEQ and WIWI will also be completed at the 6-month timepoint.

A survey link will be sent out to participants for completion of study questionnaires at all time points.

The questionnaire responses will be entered by study subjects directly into the Scribe/Labmatrix system.

Those participants who do not return an assessment within 2 weeks may receive up to 2 reminder email/telephone calls from research staff.

3.3 CALM QUALITATIVE INTERVIEW

One qualitative interview will be completed by a select number of participants (within 1-2 months) after completion of the 3rd CALM session. The time to complete the interview is approximately 15-20 minutes. Interviews will be conducted until thematic saturation is reached (i.e., adequate data has been identified and no new information is expected). Thematic saturation is estimated to be between 15-30 participants. The research team will assign the interviews to the first 15 participants starting with enrollee #5. This group of 15 will be evaluated and additional participants will be selected if saturation has not been reached.

All qualitative interviews will be audio-recorded and transcribed. Transcripts (i.e., with names, any clearly identifying information, and site-specific medical record numbers, if mentioned, will be deleted from the transcripts) will be filed according to participants' ID and also securely stored in secure servers in the Neuro-Oncology branch.

This instrument is submitted as a separate document.

3.4 STUDY CALENDAR

Procedure	*Baseline evaluation*	*CALM Therapy*	*3-month evaluation (+/- 2 weeks)*	*6-month evaluation (+/- 2 weeks)*
CALM Therapy[1]		→	→	→
Adverse Events		→	→	→
PROMIS-Depression	X		X	X
The Quality of Life at the End of Life-Cancer Scale (QUAL-EC)	X		X	X
The Death and Dying Distress Scale (DADDS)	X		X	X
Experiences in Close Relationships (ECR-M-16)	X		X	X
Clinical Evaluation Questionnaire (CEQ) [5]			X	X
MDASI-BT or MDASI-SP[2]	X		X	
EQ-5D[2]	X		X	
Qualitative Interview[3,4]		X		
WIWI[5]			X	X

1. CALM therapy includes 3-6 individual sessions delivered over 6 months. Additional sessions may be offered if clinically indicated while the participant is on the study.
2. Completed within 2 months prior to CALM therapy and any time after the 3rd CALM session while the participant is on the study. If these questionnaires are completed on 16C0151 protocol within the time frames required by this protocol, completion of these questionnaires do not need to be repeated.
3. The Qualitative Interviews will be conducted and scheduled within 1-2 months after participants' 3rd session.
4. The Qualitative Interviews will be conducted on a select number of participants until data saturation is reached (i.e., estimated to be 15-30 patients).
5. The CEQ and WIWI will be completed at 3 months with 6 month completion if more than 3 sessions are completed.

3.5 COST AND COMPENSATION

3.5.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. However, subjects on this study are required to provide the required internet access and may in some cases incur additional charges from their providers.

3.5.2 Compensation

Participants will not be compensated on this study.

3.5.3 Reimbursement

Participants will not be reimbursed on this study.

3.6 OFF-STUDY CRITERIA

- Completion of treatment and follow up
- Participant noncompliance
- Participant requests to be withdrawn from the study
- Lost to follow-up
- Death
- PI decision to close the study
- Permanent loss of ability to consent

3.6.1 Lost to Follow-up

A participant will be considered lost to follow-up if he or she is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to participate in a required CALM session:

- Research staff will attempt to contact the participant and reschedule the missed session within 14 days of the originally scheduled time and counsel the participant on the importance of maintaining the assigned session and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, an email will be sent to the participant). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of loss to follow-up.

4 CONCOMITANT MEDICATIONS/MEASURES

No restrictions on participant's current medication.

5 BIOSPECIMEN COLLECTION

N/A

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing the entry of data into a 21 CFR Part 11-compliant data capture system provided by the NCI CCR and for ensuring data accuracy, consistency, and timeliness. The principal investigator, associate investigators/research nurses, and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

Participant's disease status at the time of study entry will be identified in the database as 1) newly diagnosed or 2) currently recurrent or 3) on surveillance.

Should a participant withdraw from the study, it will be confirmed if they wish to withdraw from 1) all components of the study; 2) completing questionnaires but wish to continue therapy sessions; 3) therapy sessions, but willing to complete questionnaires.

All psychiatric adverse events regardless of severity will be followed until return to baseline or stabilization of event.

Document AEs from the first study intervention, baseline evaluations through study participation.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in section **7.2.1**.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

The PI will share coded linked human data generated in this research for future research

- in an NIH-funded or approved public repository clinicaltrials.gov
- in BTRIS
- in publication and/or public presentations

at the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

Genomic Data Sharing Policy is non-applicable for this protocol as no genomic data are analyzed.

6.3 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each participant while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.

A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

7 NIH REPORTING REQUIREMENTS / DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reviewed by the OHSRP in the NIH eIRB system will also be reported to the NCI Clinical Director/designee; therefore, a separate submission for these reports is not necessary.

7.4 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

The clinical research team will meet on a weekly basis when participants are being actively treated on the trial to discuss each participant.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each participant to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL HYPOTHESIS

Primary Endpoint:

- To demonstrate the effects of the CALM intervention in the reduction of depressive symptoms using the PROMIS-Depression scale in PCNST participants from baseline to 6 months.

Secondary Endpoints:

- To demonstrate the short-term effects of the CALM intervention in the reduction of depressive symptoms using the PROMIS-Depression scale in PCNST participants from baseline to 3 months.
- To determine the effects of the CALM intervention on death anxiety using the Death and Dying Distress Scale at both 3 and 6 months, compared to baseline.
- To describe the feasibility of implementing CALM remotely in a sample of PCNST participants.

Exploratory Objectives:

- To determine the effects of the CALM intervention on psychological well-being as measured by the Quality of Life Cancer Scale (QUAL-EC) and the modified brief Experiences in Close Relationships (ECR-M-16) questionnaire at both 3 and 6 months, compared to baseline
- To explore the effects of the CALM intervention, more specifically the relationship between distress and symptom burden as measured by the M.D. Anderson Symptom Inventory-Brain tumor (MDASI-BT) or M.D. Anderson Symptom Inventory-Spine Tumor (MDASI-SP) symptom severity and symptom factor scores.
- To explore the effects of the CALM intervention on the relationship between distress and symptom interference as measured by the MDASI-BT or MDASI-SP interference scores.

  To explore the effects of the CALM intervention on health status as measured by the EQ-5D and CEQ.

8.2 SAMPLE SIZE DETERMINATION

The primary objective of this study is to demonstrate the reduction of depressive symptoms from baseline to 6 months using CALM in PCNST participants. Based on the previous study, we expect a mean difference reduction in depressive symptoms of 1.8 with a standard deviation of the difference of 5.7. To detect this difference, we need 80 participants using a 2-tailed test at 5 significance level and 80% power. To account for estimated attrition of 20%, recruitment of 100 participants to have 80 evaluable participants.

8.3 STATISTICAL ANALYSIS

8.3.1 Analysis of the Primary Endpoint

To demonstrate the effect of CALM on depressive symptoms using PROMIS-Depression, we will perform a paired t-test from baseline to 6 months using a 2-tailed test at a 5% significance level. One interim analysis is planned when half of the participants have undergone CALM treatment. The study will be stopped early if the absolute nominal statistic for paired differences in depressive symptoms is larger than 2.782 (alpha=.0054) to claim the benefit of CALM. At the end of the study, CALM treatment will be claimed to be a success if the absolute nominal critical point is larger than 1.967 (alpha=.0492). The stopping boundary is based on the O'Brien-Fleming method with 2 interim analyses.

8.3.2 Analysis of the Secondary Endpoints

This study will report feasibility metrics associated with the implementation of CALM remotely in a primary central nervous system tumor population, including compliance, eligibility, accrual, adverse effects, study completion, and participant satisfaction with the intervention. If attrition is less than 20% of enrolled participants, this study is considered feasible. If 50% of participants report satisfaction with the intervention on the WIWI it will be considered feasible.

To describe the effects of the CALM intervention on death anxiety we will calculate total scores, subscale scores, and/or t-scores (if applicable) for the Death and Dying Distress completed at varying time points (baseline, month 3, and month 6). This data will be summarized by time point quantitatively and graphically. To quantify the immediate CALM effect, we will calculate the effect size difference between baseline scores and month 3. To quantify the long-term CALM effect, we will calculate the effect size differences between baseline and month 6.

Previous data on death anxiety reported by advanced cancer participants who underwent CALM showed a reduction of 8 (SD of the difference=15.7). With 80 participants, we have 99% power to detect this difference using a two-tailed test at a 5% significance level. To determine whether there is sufficient power to demonstrate reductions in psychological distress and psychological well-being, we need preliminary data on these variables that is due to the CALM treatment. In the absence of preliminary data, we cannot provide statements about the statistical power of these secondary endpoints. However, this study will generate preliminary data that will inform future studies.

To evaluate the feasibility of implementing CALM remotely, we will use descriptive statistics to summarize information, including rates of compliance and attrition, and participant satisfaction. This will be evaluated at the interim analysis using the same percentages outlined for the final analysis. The quantity of missing data, the variability of the data over time, and trends over time will be especially important to report to assess the feasibility of CALM. We will report participant satisfaction with the CALM experience using the responses from the WIWI instrument and thematic analysis of participant responses from the interviews. Participant's responses will go through a multi-stage process of categorizing and coding to identify themes associated with the participants experience with the CALM intervention. Results of the analysis will be reported out separately.

We will consider the study to be feasible if the following criteria are met:

- Accrual: Recruitment of 100 participants to have 80 evaluable participants in two years and less than 20% of eligible participants unable to participate due to lack of electronic devices (computer, smartphone, or iPad).
- Compliance: at least 80% of participants completing the outcome measures at all time points

Tolerability and acceptability will be assessed through the WIWI.

8.3.3 Exploratory Analyses

To determine the effect of the CALM intervention on well-being, we will calculate effect size differences in well-being using between baseline and months 3 and 6.

To explore the effects of the CALM intervention on symptom burden and interference, we will report subscale scores for the MDASI-BT and MDASI-SP and the proportion of participants with 5 or greater (moderate to severe) and 7 or greater (severe) ratings on the 0-10 numeric rating scale of each symptom items for each time point. To quantify the immediate CALM effect, we will calculate the effect size difference between baseline scores and month 3. To quantify the long term CALM effect, we will calculate the effect size differences between baseline and month 6. We will fit a linear mixed model with participants as a random effect and time as a fixed effect using MDASI-BT and MDASI-SP subscale scores as a dependent variable.

To explore the effects of the CALM intervention on health status, we will perform linear mixed models and effect size calculations on health status using raw and subscale scores from the EQ-5D. To quantify the immediate CALM effect, we will calculate the effect size difference between baseline scores and month 3. To quantify the long-term CALM effect, we will calculate the effect size differences between baseline and month 6. We will fit a linear mixed model with participants as a random effect and time as a fixed effect using EQ-5D as a dependent variable.

9 HUMAN SUBJECTS PROTECTIONS

9.1 RATIONALE FOR SUBJECT SELECTION

No gender, racial or ethnic groups will be excluded from participation in this trial. Participants who do not speak English will be excluded because some of the questionnaires used in this study are only available in English.

We are not enrolling caregivers into the study because we do not plan to evaluate their own problems and/or collect their data. If the patient asks for them to be part of the session the caregiver can be included in the discussion to understand their relationship with the participant and validate the participant's answers.

9.2 PARTICIPATION OF CHILDREN

This protocol will not include those less than 18 years old since the participants will be recruited and enrolled from Natural History Protocol (#16C0151) and the participant population is 18 and over.

9.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to provide consent are excluded from enrolling in the protocol. However, it is possible that subjects enrolled in the protocol may permanently lose the capacity to consent for themselves during the course of this study because they have primary central nervous system tumors. In the event this occurs, the subjects will be taken off study as they would not be able to benefit from therapy or complete questionnaires.

9.4 RISK/BENEFIT ASSESSMENT

9.4.1 Known Potential Risks

There are potential risks to psychotherapy. People may initially feel worse as the therapy progresses. In rare cases, psychotherapy may even trigger some people to have thoughts about wanting to hurt themselves or end their lives. In previous studies, there was no negative feedback from participants about their experiences of CALM and no withdrawals from treatment based on dissatisfaction with it. We believe CALM therapy will pose only minimal risk to the study subjects.

9.4.1.1 Risk of questionnaires

Questionnaires may contain questions that are sensitive in nature. To minimize this risk, participants are asked to only answer questions they are comfortable with when asked to complete questionnaires.

9.4.1.2 Risk of losing data

There is a risk that data obtained during this study, or trait can be released to members of the public, insurers, employers, or law enforcement agencies. Although there are no plans to release results to the participants, family members, or health care providers, this risk will be included in the informed consent document.

9.4.1.3 Risk of interviews

Some of the questions the interviewer will ask may be upsetting or uncomfortable to the participant. To minimize this risk, participants do not have to answer any questions they do not want to answer and can stop the interview at any time. There is also a risk that the personal, identifiable information collected during this study, might be accessed by people who are not supposed to see this information. To minimize this risk, interviews will be saved in a password protected audio file stored behind the NIH firewall. Accessed only by authorized study personnel. These risks will be included in the consent form.

9.4.2 Known Potential Benefits

Research conducted over the past decade has shown that CALM is a feasible, acceptable, and effective therapy for participants with advanced or metastatic cancer. We do believe that this therapy may help participants to reduce psychological distress and promote well-being. Information from this study may be used to help PCNST participants in the future, as study results may provide doctors with a better understanding of PCNST treatment effects, symptoms, and quality of life.

9.4.3 Assessment of Potential Risks and Benefits

Participation in the study is expected to benefit participants by reducing psychological distress and promoting their well-being. Data collected will help provide the medical community with a greater knowledge of PCNST symptoms related to psychological distress. It is not likely that there will be significant medical risks associated with participating in this study since there are no study-required drug interventions. Study subjects will participate in psychological sessions and will be asked to answer a set of questionnaires. There is a potential loss of privacy; however, all possible precautions will be taken to respect the subject's privacy and the confidentiality of their information

9.5 CONSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided as a physical or electronic document to the participant for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts, and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members, and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry into the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per the discretion of the designated study investigator and with the agreement of the participant. Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/, when in-person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or as described below, with a manual (non-electronic) signature on the electronic document. When required, witness signature will be obtained similarly as described for the investigator and participant.

Manual (non-electronic) signature on electronic document:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will use the following to obtain the required signatures:

- Adobe platform (which is not 21 CFR Part 11 compliant); or,
- iMedConsent platform (which is 21 CFR Part 11 compliant)

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations (if remote consent); the same screen may be used when in the same location but is not required.

Both the investigator and the participant will sign the document using a finger, stylus, or mouse.

Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

10 REGULATORY AND OPERATIONAL CONSIDERATIONS

10.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending, or terminating party to study participants, investigator. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping

- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy IRB.

10.2 QUALITY ASSURANCE AND QUALITY CONTROL

The NCI site will perform internal quality management of study conduct, data collection, documentation and completion as described in Section 6 Data Collection.

Quality control (QC) procedures will be implemented as follows:

Informed consent --- Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

Source documents and the electronic data --- Data will be captured and entered directly into the study database. To ensure accuracy site staff will compare a representative sample of source data against the database, targeting key data points in that review.

Intervention Fidelity — Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring CALM intervention are described in Section 1.2.2, CALM Psychotherapy.

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Following written Standard Operating Procedures (SOPs), if this study is monitored, the monitors will verify that the clinical trial is conducted, and data are generated, collected, documented (recorded), and reported in compliance with the protocol, International Council for Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices [GMP]).

Should independent monitoring become necessary, the PI will provide direct access to all trial related source data/documents, and reports for the purpose of monitoring and auditing by regulatory authorities.

10.3 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry or device, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National Cancer

Institute has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.4 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, and their staff. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

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

The study monitor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the/each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB or Institutional policies.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site(s) and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NIH.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

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