MCC-21-18040
NCT 05087095
Managing Distress in Malignant Brain Cancer – Patients with Brain Metastases
Approval: 1/7/2022

MCC-21-18040
NCT 05087095
Managing Distress in Malignant Brain Cancer – Patients with Brain Metastases
Approval: 1/7/2022

SIGNIFICANCE

Brain tumors originate either in the brain itself (primary brain tumor, PBT) or develop secondarily to another cancer that has spread to the brain (brain metastasis, bMET). bMET is much more common than PBT, with 10-30% of all cancers spreading to the brain (1). At least 170,000 Americans will be diagnosed with bMET each year (1, 2)—nearly double the incidence rate of PBT—and this figure is likely an underestimate (3). The symptoms associated with brain cancer are numerous and include fatigue, sleep disturbance, headache, nausea, seizure, cognitive changes, and neurologic symptoms, such as dizziness, difficulty with balance, sensory problems, and numbness/tingling.[6] Most patients endorse multiple symptoms of at least moderate severity (5), and the vast majority require some form of rehabilitation therapy (6). Compared to other cancer populations, individuals with brain cancer are less likely to be employed (7, 8) and more likely to be divorced (9). Activities of daily living that promote independence, such as self-care, locomotion/mobility, and driving can be affected by the tumor itself, treatment, or both (10, 11).

Military service members and Veterans are a particularly vulnerable group and may be at increased risk for brain cancer. Brain cancer is the third most common cause of cancer death among active-duty service members (SMs) in the US military (12). Although PBT accounts for less than 1% of all cancers treated in the US Veterans Affairs Health Care System (VA) (13), evidence suggests that individuals with a history of military service are at elevated risk for PBT compared to other occupations, because of combat, exposure to electromagnetic fields / radiation (14, 15), or toxic agents during chemical warfare (16, 17). Further, with respect to bMET, the most frequently diagnosed cancers in the VA are those most likely to result in bMET: lung, colon, kidney, and melanoma (4). Despite this increased risk, Veterans who receive VA care for brain cancer may experience more favorable mortality outcomes compared to the general population: In a matched case analysis, SMs with PBT demonstrated a survival advantage across age, race, histological, and treatment history strata compared to civilians with PBT (18). Taken together, these data suggest that while military populations may be at greater risk of developing brain cancer, they may also experience longer survival periods—making preservation of life quality particularly important among SMs and Veterans with brain cancer. Of particular relevance to military populations is the finding that a brain cancer diagnosis is associated with increased risk of posttraumatic stress disorder (PTSD) and suicide in the first year following treatment (19). Up to 67% of Veterans with cancer report symptoms of PTSD brought on by their experience with cancer (20) and since 2008, the number of Veterans with completed suicides have exceeded 6,000 annually; an average rate of 16-20 per day, respectively (21). Depression, PTSD, and substance dependence are all major risk factors for suicide in Veterans (22-24). Importantly, all of these factors have been shown to be improved by behavioral health interventions (25-27), including in patients with advanced cancer (25, 26).

Treatment options for individuals with brain cancer are lacking. Medical advances have nearly doubled median survival rates over the past decade (28, 29). However, there is still no cure for malignant brain cancer. The median overall survival for patients with bMET is now approximately 6 months, with 1- and 2-year survival rates at 8.3% and 1.4%, respectively (30). Medical interventions targeting amelioration of PBT and bMET are associated with a range of adverse effects, including cognitive decline and fatigue, compounding the symptoms of the disease itself. Given this poor prognosis, medical management often focuses on symptom alleviation (e.g., the provision of steroids to reduce brain swelling, anticonvulsants to reduce seizure frequency) (31). Tailored, evidence-based behavioral health interventions for SMs, Veterans, their beneficiaries, and civilians with brain cancer that focus on preparation for living with a brain tumor, its treatment, and the fatal disease trajectory are not only essential for mission readiness, but are also mission critical.

Brain cancer is associated with significant distress and reduced quality of life. In the absence of curative medical treatments for malignant PBT and bMET, care must include a focus on increasing psychological preparedness and improving quality of life. Nearly all patients with PBT (93%-95%) report symptoms of depression (32, 33), with rates of clinical diagnoses greater than both other oncology populations and the general population (22%- 41% v. 13% v. 7%, respectively) (33-38). Our own preliminary data demonstrate that those with PBT endorse a particular type of distress—death anxiety—at a drastically higher rate than other cancer populations (81% v. 32%) (39). Death anxiety refers to fear and preoccupation with thoughts of death and dying that may interfere with individuals' daily functioning. Anxiety regarding death is understandable among those with brain cancer given the uncertain disease trajectory, lack of curative treatment, potential loss of functioning, and the inherent existential nature of brain cancer itself (40). In advanced cancer patients, behavioral health interventions that focus on increasing preparedness, finding meaning, and understanding disease trajectory have been shown to reduce distress, and improve mood and life quality (25).

Individuals with brain cancer are significantly underrepresented—and often excluded—from behavioral health

intervention trials that could improve their preparedness and life quality. Despite documented high rates of distress among those with PBT and bMET, little is known about the trajectory of this distress, its correlates, or effective treatments. Our research team recently conducted a systematic review of the extent to which individuals with brain cancer are included in psycho-oncology research focused on death-related distress. Results revealed that this patient population represented only 0.18% of participants included in such studies (41). Frequently, this omission is not due to oversight, but rather is a specific exclusion criterion at least partly based on the unsubstantiated assumption that individuals with brain cancer are not cognitively capable of participating in such research (41). While individuals with PBT and bMET are at risk for cognitive decline, only a small sub-sample demonstrate cognitive impairment to an extent that would exclude them from participating in intervention trials. In our own research, we found that the vast majority (91%) of patients with PBT were cognitively eligible (66% fully functional, 25% with mild cognitive impairment) and only 9% performed in an ineligible range reflective of dementia (42). In short, the need to include SMs, Veterans, their beneficiaries and civilians with PBT and bMET in behavioral health intervention research is clear, and their exclusion represents an injustice that sustains a critical gap in clinical knowledge and services for those who are most in need of support.

Study Treatment/ Behavioral Health Intervention.
An evidence-based, effective intervention to address distress in advanced cancer exists but has never been studied in SMs, Veterans, their beneficiaries or civilians with brain cancer. Though cognitive behavioral therapy is effective for a variety of psycho-oncology concerns, it is not effective for treating depression and related symptoms in individuals with advanced cancer (43-46). Similarly, psychopharmacological approaches are of limited benefit and are contraindicated for individuals with PBT or bMET; antidepressant use is associated with lowered seizure thresholds, cognitive decline, worsened fatigue and tumor recurrence (47, 48).

An alternative intervention, **Managing Cancer and Living Meaningfully (CALM)**, was designed to specifically address the inevitable challenges patients with advanced cancer face. CALM is a brief, individual, manualized, behavioral health intervention developed by palliative care and psycho-oncology leaders to provide hope, manage distress, increase preparedness, and improve quality of life (25, 49, 50). CALM optimally consists of six individual sessions of 45 to 60 minutes, delivered over a three- to six-month period. CALM sessions address four broad and interrelated domains found to be important and relevant in this population: (1) symptom management and communication with healthcare providers, (2) changes in personal relationships, (3) sense of meaning and purpose, and (4) the future, hope and mortality (**Figure 1**). These domains are addressed with all patients at some point during the intervention, although the sequence and relative emphasis on each domain vary, depending on their urgency and relative importance to each individual participant. CALM research conducted over the past decade has shown CALM to be feasible and acceptable (51-53), and a large recent RCT has shown that CALM is effective in treating and preventing depression at 3 and 6 months compared with usual care (25). Notably, CALM is the only intervention shown to significantly decrease death anxiety (54). No adverse events were reported during the RCT, including increased risk for suicide. However, previous studies have not targeted SMs, Veterans, their beneficiaries or civilians with brain cancer during CALM trials.

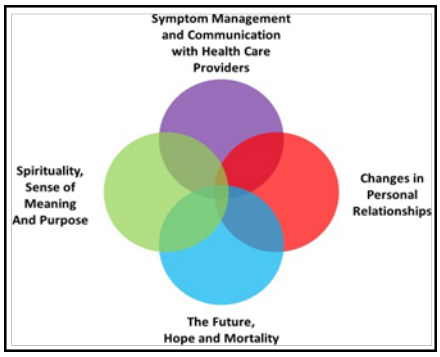


Figure 1. Domains of Calm

Primary Outcomes

1. Assess the Need for Adaptations to the CALM Intervention as Measured by the Applicability of the 4 CALM Domains
2. Feasibility of CALM Intervention in the Proof of Concept Project as Measured by the Rates of Participant Screening, Eligibility, and Consent.
3. Feasibility of CALM Intervention in the Proof of Concept Project as Measured by Attendance at CALM Sessions
4. Feasibility of CALM Intervention in the Proof of Concept Project as Measured by the Rates of Post-session Assessment

Completion

5. Feasibility of CALM Intervention in the Proof of Concept Project as Measured by Post-Intervention Assessment Completion

6. Benefit of Intervention in the Proof of Concept Project as Measured by Participant Responses to Researcher-developed Questions as Part of the Exit Interview

Primary Endpoints

1. Rate of domains applicability

2. % of participant Screening, Eligibility, and Consent

3. % of attendance at CALM Sessions

4. % of post-session assessment completion

5. % of post-intervention assessment completion

6. Rate of intervention benefit

RESEARCH STRATEGY AND FEASIBILITY

Approach. A mixed-methods approach, utilizing the NIH Science of Behavior Change (SOBC) supported ORBIT model[43,44] has been chosen for this study. The ORBIT model begins with a theory grounded in behavioral science about the mechanisms of behavior change (Phase I), and develops an intervention in small incremental steps, paying attention to tailoring, acceptability, and testing efficacy of early outcomes using smaller experiments (Phase II), before embarking on a randomized controlled trial (Phase III).

Study Population. Adult patients with brain metastases diagnosis.

Inclusion Criteria. This study will consider for enrollment individuals of all genders, ethnic, racial, and socioeconomic backgrounds. Participants must: (1) have a confirmed brain met diagnosis via medical records, (2) be a minimum of 2 weeks post-surgical cranial resection or biopsy (if applicable), (3) be primarily English speaking, (4) be age 18+, (5) obtain $\geq$20 on Telephone Interview for Cognitive Status, (6) have current elevated depression (Patient Health Questionnaire-9 Item [PHQ9] $\geq$10) or death anxiety symptoms (Death and Dying Distress Scale [DADDS] $\geq$15),[23] and (6) have reliable internet connection.

Exclusion Criteria. This study will exclude participants with: (1) Major communication difficulties as determined by the research team which would prohibit psychotherapeutic interaction, (2) inability to meet with interventionist via an electronic device for telehealth intervention sessions, or (3) inability to provide informed consent.

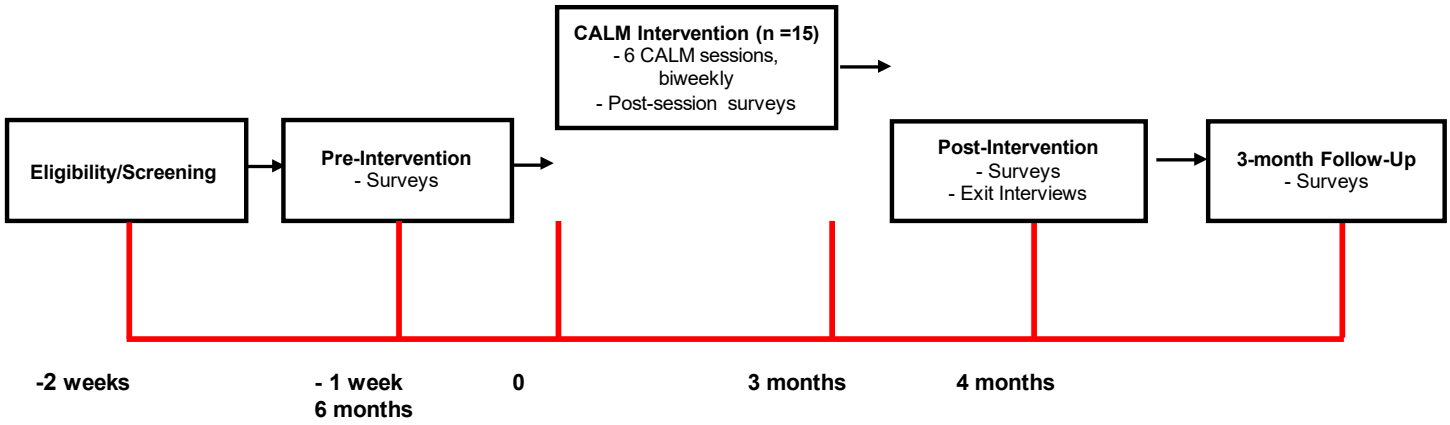
VCU Recruitment. VCUHealth treats approximately 400 individuals with bMET annually. Participants can be directly referred by their neuro-oncology clinical team. Flyers will also be email or mailed to those seen within VCUHealth in the last year. If patients are interested in participating, a telehealth screening interview will be scheduled. Trained study staff will screen for eligibility. If eligible, individuals will have the study described to them. Interested individuals will be emailed and asked to read the consent form and encouraged to ask any questions. They will be informed that their decision to (or not) participate will not affect their care at any VCU facility. Once all questions are answered, interested individuals will be asked to sign the consent form electronically.

Scientific Rigor. To parallel the multi-phase drug development scientific process, including intervention development and dose-responsetesting (Phase I), feasibility and acceptability evaluations (Phase II), and eventual Phase III efficacy trails, the NIH SOBC ORBIT model was selected to guide this project.[43] To promote a robust and unbiased approach, we will: (1) use validated measures, (2) have a non-clinical research assistant (RA) conduct eligibility screening and consent to reduce coercion, and (3) have the RA collect participant measures and conduct exit interviews.

AIM 1: Proof-of-Concept Trial Design. Using the ORBIT model, we will initially conduct a 1-year Phase IIa/b *Proof-of-Concept Trial* to guide CALM implementation for individuals with PBT. Within two weeks before and after the intervention and 3 months post-intervention, participants will be asked to complete self-report surveys of behavioral and psychological variables

via a secure online data collection system (REDCap). Participants will be offered a $20 gift card for completing these surveys across each of the 3 timepoints (pre-intervention, post-intervention, follow-up). If paper copies of the questionnaire are preferred by the participant, these can be mailed and the RA will input any data into REDCap upon return. Six sessions of CALM therapy will be provided at no cost to participants. After each intervention session, participants will be sent a link for a brief post-session satisfaction survey via secure email link. Participants will rate 1) topic applicability; 2) perceived benefit of session; 3) comfort with interventionist(s); and 4) overall satisfaction. Participants who withdraw will be contacted and asked open-ended questions on reasons for termination and suggestions for improvement.

Within one month of intervention completion, the RA will conduct individual exit interviews by phone, which will be audio recorded for verbatim transcription. Interviews will assess length and number of sessions, content applicability, recommended modifications, helpful and unhelpful aspects of sessions, perceived benefits, overall satisfaction, and suggestions for improvement. This will inform treatment preferences, intervention adaptations, and overall satisfaction. Our team has used these survey and interview measures with success in prior treatment development trials.[49,50] At any time during the intervention, participants considered by the therapist to be at acute risk for suicide, or who demonstrate significant worsening of depression or other psychiatric co- morbidities that require treatment, will be referred for psychiatric assessment and treatment in the Department of Psychiatry. This may include pharmacotherapy or other psychiatric interventions.



Evaluation Metrics

Domain	Metric	Target
Recruitment Feasibility	• Screening rate	70%
	• Eligibility rate	50%
	• Reasons for ineligibility	--
	• Enrollment rate	30%
Acceptability of Procedures	• Baseline questionnaire adherence	75%
	• Post-session survey adherence	60%
	• Post-CALM questionnaire adherence	60%
	• Exit interview adherence	60%
Intervention Acceptability	• Intervention Completion of Trial Initiators	70%
	• Reason for withdrawal	--
	• Intervention satisfaction survey benefit rating	Rating $\geq$ 4/5
	• CEQ rating (preliminary)	$\geq$14

Psychological Distress and Life Quality Outcome Measures

Measure		Items	Distress Descriptors	
Patient Health Questionnaire	PHQ-9	9	0-5	Minimal
			5-9	Mild
			10-14	Moderate
			15-19	Moderately Severe
			20-27	Severe
Death and Dying Distress Scale	DADDS	15	0-24	Low
			25-46	Moderate
			47-75	Severe
Generalized Anxiety Disorder	GAD-7	7	0-4	Minimal

			5-9 10-14 15-21	Mild Moderate Severe
Quality of Life at the End-of-Life Cancer Scale	QUAL-EC	17	0-68	--
Functional Assessment of Chronic Illness Therapy – Spiritual Wellbeing Scale	FACIT-sp	12	0-48	--
Fear of Cancer Recurrence	FCR-7	7	≥17 ≥27	60th percentile 90th percentile
Post-Traumatic Stress Disorder Checklist	PCL-5	20	≥31	Probable PTSD
Suicidal Ideation	PHQ-9	1	0-3	--
Tobacco, Alcohol, Prescription medication and other Substance Use	TAPS	4	0 1 2	No Use Problem Use Higher Risk

DATA ANALYSIS.

Detailed records of the number of individuals who screen, are eligible, enroll, complete assessment measures, and attend telehealth sessions will be kept. Reasons for attrition will be recorded. Individuals who "no-show" will be contacted to assess continued interest and will be rescheduled as appropriate. Each attempt to contact participants will be recorded. This information will guide future recruitment/retention and inform feasibility. Recruitment source will be tracked to determine the most fruitful strategies. We will calculate frequencies and proportions to explore preliminary feasibility outcomes and means and standard deviations or medians and interquartile ranges to assess preliminary acceptability. The two-sample t- tests and/or Mann-Whitney U-test, and chi-square tests will be used to compare eligible patients who did and did not enroll in terms of demographic, medical, and psychiatric variables. Within-group changes in behavioral and psychological variables will be explored to prepare for future pilot and efficacy trials. Thus, for each data collection time points we will calculate the mean and standard deviation of exploratory outcomes. In addition, we will calculate the correlation on the measures between time points as well as calculating the difference scores and the accompanying standard deviations.