MCC-20-16440
NCT04646213
Managing Cancer and Living Meaningfully (CALM) in Patients with Malignant Primary Brain Tumors
Approval Date: 11/19/2020

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# Notification: IRB HM20020308 Loughan - IRB Correspondence

1 message

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Thu, Nov 19, 2020 at 3:09 PM

Office of Research and Innovation

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TO: Ashlee Loughan

CC: Alexandria Davies

FROM: VCU IRB Panel A

RE: Ashlee Loughan ; IRB HM20020308 Managing Cancer and Living Meaningfully (CALM) in Primary Brain Tumor Patients

On 11/19/2020, the referenced research study was ***approved*** by expedited review according to 45 CFR 46.110 by VCU IRB Panel A .This study is approved under :

**Expedited Categories**

| | |
|---|---|
| Category 5 | Involves materials (data, documents, records, or specimens) that have been collected or will be collected solely for nonresearch purposes including medical treatment or diagnosis. |
| Category 6 | Involves the collection of data from voice, video, digital, or image recordings made for research purposes. |
| Category 7 | Is research that will be performed on individual or group characteristics or behavior OR will employ a survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. |

The VCU IRB approved a request for a *partial waiver* of authorization for the use and disclosure of protected health information (PHI). The VCU IRB determined that documentation you provided satisfies the following criteria:

1. The use or disclosure of the PHI involves no more than minimal risk to the privacy of individuals based on the presence of the following elements:
   - An adequate plan to protect health information identifiers from improper use and disclosure.
   - An adequate plan to destroy identifiers at the earliest opportunity consistent with conduct of the research (absent a health or research justification for retaining them or a legal requirement to do so).
   - Adequate written assurances that the PHI will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the HIPAA Privacy Rule.
2. The research could not practicably be conducted without the waiver.
3. The research could not practicably be conducted without access to and use of the PHI.

The information found in the electronic version of this study's smart form and uploaded documents now represents the currently approved study, documents, informed consent process, and HIPAA pathway (if applicable). You may access this information by clicking the Study Number above.

**COVID-19 Notice**

In the context of the COVID-19 pandemic, the IRB expects the research will proceed in accordance with other institutional policies and as outlined in this submission and if applicable, in the study's COVID-19 Contingency Protocol. IRB approval does not necessarily mean that your research may proceed. For more information on investigator responsibilities and institutional requirements, please see https://research.vcu.edu/covid-19.htm

The Principal Investigator is also reminded of their responsibility to ensure that there are adequate resources to carry out the research safely. This includes, but is not limited to, sufficient investigator time, appropriately qualified research team members, equipment, and space. See WPP #: IX-1 Principal Investigator Eligibility and Statement of Responsibilities

**A status update for this study is due on 11/19/2021. Ongoing continuing review is not required.** However, VCU Policy and Procedures require status updates on at least an annual basis. Status Update notices will be sent to you prior to the scheduled due date.

If you have any questions, please contact the Office of Research Subjects Protection (ORSP) or the IRB reviewer(s) assigned to this study.

The reviewer(s) assigned to your study will be listed in the History tab and on the study workspace. Click on their name to see their contact information.

**Attachment – Conditions of Approval**

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**Conditions of Approval for Expedited and Full Board Studies** (version 1/21/2019)

In order to comply with federal regulations, industry standards, and the terms of this approval, the investigator must (*as applicable*):

1. Conduct the research as described in and required by the IRB-approved protocol/smartform.
2. Obtain approval from the VCU IRB before implementing any changes in the approved research unless such changes are necessary to protect the safety of human research participants.
    - Report any departure from the approved protocol/smartform or documents to the VCU IRB immediately through a report submission.
    - Obtain approval from the VCU IRB before use of any advertisement or other material (print or electronic) for recruitment of research participants.
    - Obtain approval from the VCU IRB before implementing any changes related to the future sharing of individual-level research data.
3. Obtain informed consent from all prospective participants or the participant's legally authorized representative without coercion or undue influence, and provide the potential participant sufficient opportunity to consider whether or not to participate (unless a Waiver of Consent was specifically approved).
    - Obtain informed consent using only the most recently approved consent document (unless a Waiver of Consent was specifically approved).
    - Provide non-English speaking participants with a written translation of the approved consent document (or a translated version of the Short Form Consent document) in language understandable to the research participant. The IRB must approve the translated version and/or the use of a short form consent process prior to use.
4. Monitor all problems (anticipated and unanticipated) associated with risk to research participants or others.
5. Report all Unanticipated Problems (UPs) involving risk to participants or others following the VCU IRB requirements and timelines detailed in WPP VII-6.
6. Respond promptly to all inquiries from the VCU IRB and Office of Research Subjects Protection concerning the conduct of the approved research.

*The VCU IRBs operate under the regulatory authorities as described within:*

- *U.S. Department of Health and Human Services Title 45 CFR 46, Subparts A, B, C, and D (for all research, regardless of source of funding) and related guidance documents.*
- *U.S. Food and Drug Administration Chapter I of Title 21 CFR 50 and 56 (for FDA regulated research only) and related guidance documents.*
- *Commonwealth of Virginia Code of Virginia 32.1 Chapter 5.1 Human Research (for all research).*

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**IRB PERFORMANCE SURVEY:**
We value your feedback! Please take 1-2 minutes to complete the IRB Performance Survey in relation to your experience with this

approved submission: https://IRBperformancesurvey.questionpro.com

**Managing Cancer and Living Meaningfully (CALM) in Primary Brain Tumor Patients**

## SIGNIFICANCE

**Brain cancer is associated with disproportionate financial impact, symptom burden, and functional impairment.** Brain cancer is the third most common cancer diagnosed in young adults and the eighth-most common among those age 40 and older.[1] Estimates place the prevalence rate for PBT in the United States (US) at 0.21% of the population (more than 700,000 affected individuals), with an additional 87,000 individuals diagnosed in 2020 alone.[2] Brain tumors incur both the highest per-patient initial care cost (mean net cost approaching $150,000) and the highest per-patient last-year-of-life care cost (mean net cost ranging from $135,000 to $210,000) relative to other cancers.[3] Further, 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.[4] Most patients endorse multiple symptoms of at least moderate severity,[4] and the vast majority require some form of rehabilitation therapy.[5] Compared to other cancer populations, individuals with brain cancer are less likely to be employed[6,7] and more likely to be divorced.[8] 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.[9,10]

**Treatment options for individuals with brain cancer are lacking.** Despite medical advances that have nearly doubled median survival rates over the past decade,[11,12] there is still no cure for malignant brain cancer. Glioblastoma multiforme, the most common type of malignant PBT, has a median overall survival rate of 15 months and a five-year survival rate of 6.8%.[2] It is estimated that over 18,000 people with a malignant PBT will die each year. Furthermore, medical interventions targeting amelioration of PBT 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).[13] Tailored, evidence-based psychosocial interventions for individuals with brain cancer have not been available.

**Brain cancer is associated with significant distress and reduced quality of life.** In the absence of curative medical treatments for malignant PBT, care must include a focus on improving quality of life and reducing psychological burden. Nearly all patients with PBT (93%-95%) report symptoms of depression,[14,15] with rates of clinical diagnoses greater than both other oncology populations and the general population (22%-41% v. 13% v. 7%, respectively).[15–20] 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%).[21] 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.[22] Distress of this kind in individuals with advanced cancer has been shown to be ameliorated by psychotherapeutic intervention.[23]

**Individuals with brain cancer are significantly underrepresented—and often purposely excluded—from behavioral and psychosocial investigations.** Despite documented high rates of distress among those with PBT, 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.[24] Frequently, this omission is not due to oversight, but rather is purposeful and based on the unsubstantiated assumption that individuals with brain cancer are not cognitively capable of participating in such research. While those individuals with PBT are at risk for cognitive decline, only a small sub-sample demonstrate cognitive impairment to an extent that would exclude them from research studies. In our own research using a common cognitive screener, the Mini Mental State Exam (MMSE), we found that the majority (66%) of patients with PBT passed this eligibility screener, with 25% performing in the range indicative of mild neurocognitive disorder (mNCD) and only 9% performing in the range reflective of dementia.[25] In short, the need for inclusion of those with PBT in research is clear, and their exclusion from

behavioral and psychosocial research represents a significant gap in knowledge. The capacity of these individuals to consent and to engage in study tasks is nuanced, highlighting the urgent need for research designed and conducted by investigators familiar with this vulnerable population and its unique challenges and considerations.[26]

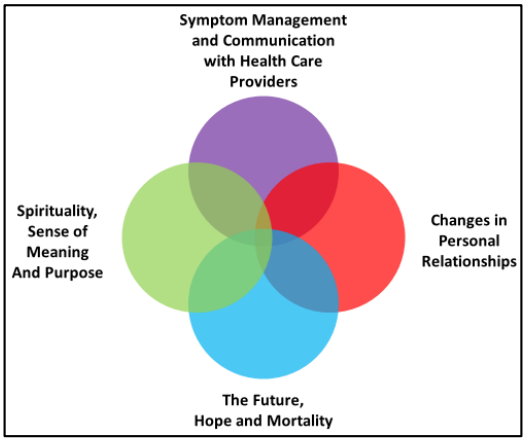


**Figure 1**. Domains of CALM

**An effective evidence-based treatment to address psychological distress in advanced cancer exists—but has never been investigated in brain cancer.** Though cognitive behavioral therapy (CBT) is effective for a variety of psycho-oncology concerns, it is less effective for individuals with advanced cancer.[27–29] Indeed, a recent large-scale randomized controlled trial (RCT) found CBT to be ineffective for treating symptoms of depression in patients with advanced cancer.[30] Similarly, psychopharmacological approaches are of limited benefit for this population, and are often contraindicated for individuals with PBT. Research further demonstrates that antidepressant use is associated with lowered seizure thresholds, cognitive decline, and worsened fatigue among individuals with PBT;[31] and, the use of antidepressants has been shown to be an independent predictor of tumor recurrence in this population.[32] An alternative intervention, Managing Cancer and Living Meaningfully (CALM), was designed to specifically address the inevitable challenges patients with advanced cancer face (**Figure 1**). CALM is a brief, individual, manualized, supportive-expressive psychotherapeutic intervention developed by leaders in psycho-oncology and palliative care.[23,33,34] CALM research conducted over the past decade has shown CALM to be feasible and acceptable,[35–37] 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.[23] Notably, CALM is the only intervention shown to significantly decrease death anxiety.[38] No adverse events were reported during the RCT, including increased risk for suicide. However, due to the perceived challenges outlined above, to date, individuals with brain cancer have been excluded from CALM trials.

## SPECIFIC AIMS

**AIMs:** To conduct a mixed-method *Phase IIa Proof-of-Concept Trial* (N = 12) with post-session surveys and individual exit interviews to guide CALM adaptation and determine preliminary feasibility and acceptability in patients with PBT.

**Exploratory AIMs**.

1. To examine within-group changes in depression, distress about death and dying, and quality of life in order to assess preliminary efficacy in this population.

## HYPOTHESES

We hypothesize that it will be feasible to recruit participants into a controlled trial, to evaluate and follow study participants and to preliminarily assess the efficacy of CALM in individuals with brain cancer. Preliminary information on CALM feasibility will be collected with regards to the ability to consent patients to the study, study session attendance, post-session assessment and follow-up assessment completion, and participant satisfaction ratings.

## 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.** Diagnosis and classification of brain cancer will be based on 2016 World Health Organization

revised criteria.[45] At VCU, 160 individuals with PBT are treated annually. For individuals with PBT, most are White (76%) followed by African American (16%) and most are men (59%). The majority fall into the younger age range (59%; 18-54 years).

**Inclusion Criteria.** This study will consider for enrollment individuals of all genders, ethnic, racial, and socioeconomic backgrounds. PBT participants must: (1) have a confirmed malignant brain cancer diagnosis via histopathology, (2) be a minimum of 2 weeks post-surgical 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 160 individuals with PBT annually. Participants will be directly referred by their neuro-oncology clinical team. Flyers will also be posted in treatment rooms. 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. We anticipate participation rates similar to those reported in prior advanced cancer behavioral health and psychotherapeutic trials, with $\geq$70% consenting to screening and $\geq$30% of eligible patients enrolling (**Table 1**).[23,35,36,40,41]

**Scientific Rigor.** To parallel the multi-phase drug development scientific process, including intervention development and dose-response testing (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 (**Figure 5**).[43] To promote a robust and unbiased approach, we will: (1) use validated measures (**Table 2**), (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 *Proof-of-Concept Trial* (N=12) to guide CALM implementation for individuals with PBT. Within one week before and after the intervention and 3 months post-intervention (if applicable given terminal illness; **Figure 6**), participants will be asked to complete self-report surveys of behavioral and psychological variables (**Table 2**) 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. Interventionists will also complete surveys at the end of each session which address: 1) topic applicability; 2) perceived participant response; 3) suggestions for improvement.

Within one month of intervention completion, the RA will conduct individual exit interviews by phone (**Figure 8**), 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.

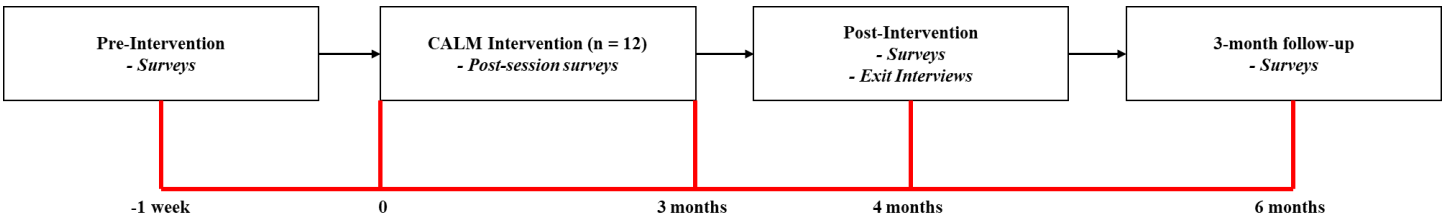


**Figure 6**. AIM 1 Intervention Timeline

**CALM Interventionists.** The PI has attended four international CALM advanced training workshops (2018: Toronto; 2019: London and Banff; 2020: Virginia). The PI is CALM certified and receives ongoing supervision from CALM founder on a bi-weekly basis to discuss cases, therapeutic fidelity, supervision of interventionists, and research procedures. The PI will supervise implementation of the CALM intervention by psychology post-doctoral and doctoral trainees. All interventionists will also have attended at least one 3-day CALM training workshop and participate in ongoing weekly supervision.

**Assessment Measures.**

**Covariates.** Baseline self-report data will include: age, gender, ethnicity, race, educational status, employment, marital and parental status, history of substance abuse and/or mental health history (psychiatric diagnoses, suicidal ideation), and self-reported social support and spirituality beliefs. We will extract the following data from medical records: time since diagnosis, tumor characteristics and treatment, seizure history, and psychopharmacological medication history. Patients' oncologists will report on estimated prognosis. Additional psychological intervention (e.g., psychotherapy, pastoral care, social work) and/or psychopharmacological medication use will also be tracked throughout the intervention and follow-up time period.

**Table 1**. *Primary Outcomes*

| **Feasibility*** | |
|---|---|
| Recruitment | ≥70% consent to screening; ≥30% of eligible enroll |
| Eligibility | Reasons for ineligibility, reasons for refusal, characteristics for refusers |
| CALM intervention | ≥60% session attendance; ≥70% post-session assessments completed; ≥60% follow-up assessments completed |
| **Acceptability*** | |
| CALM intervention | Session ratings of: satisfaction, helpfulness, enjoyment, relevance, utility (Likert Scale; 1=not at all, 5=very much; M≥4 post-session surveys); overall program satisfaction (M≥4); ≥75% would recommend program to others (post-intervention survey); likes, dislikes, adaptations, future suggestions (exit interview) |

Note. M = mean; *based on CALM trial data[23,35,36] and additional intervention studies of patients with advanced disease[40–42]

**Table 2**. *Exploratory Outcomes*

| Variable | Measurement | Minutes to Complete |
|---|---|---|
| Depression | Patient Health Questionnaire – 9 Item (PHQ9)[53]* | 2 – 5 |
| Generalized Anxiety | Generalized Anxiety Disorder – 7 Item (GAD7)[54]* | 2 – 5 |
| Death Distress | The Death and Dying Distress Scale (DADDS)[55]* | 5 – 10 |
| Fear of Cancer Recurrence | Fear of Cancer Recurrence - 7 Item (FCR7)[56] | 2 – 5 |
| Attachment | Experiences in Close Relationships Inventory (ECR-M-16)[57]* | 5 – 10 |
| Quality of Life | Quality of Life at the End of Life-Cancer Scale (QUAL-EC)[58]* | 5 – 10 |
| Suicidal Ideation | Patient Health Questionnaire – Item 9 (PHQ9)[53]* | -- |
| Clinical Evaluation | Clinical Evaluation Questionnaire (CEQ)[59]* | 2 – 5 |

Note. *Measures used in the CALM RCT

**DATA ANALYSIS.**

**Primary Outcomes.** 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 (**Table 1**). 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.

**Exploratory Outcomes.** 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.

**POTENTIAL CHALLENGES AND SOLUTIONS**

Our previous track record of research accomplishments clearly demonstrates our capacity to conduct the proposed research. The proposed qualitative methods will ensure that intervention components are appropriately adapted and aligned with patient preferences and capabilities. If enrollment is less than expected, recruitment will be expanded to greater Richmond community hospitals with which the PI has a long-standing collaborative relationship with. If eligibility rates are less than expected, we will consider enrolling individuals with high-risk grade II PBT. If intervention adherence is low, we will aim to align appointments with neuro-oncology clinic days and provide the option for in-person CALM sessions for those unable or unwilling to participate in an online intervention. Attrition due to disease progression is a concern. If necessary, additional participants will be recruited. All visits are being scheduled and completed using a telehealth format as to negate in-person safety issues with COVID-19. If telehealth is not an option for an individual, we can consider in-person clinic visits following all Centers for Disease Control and Prevention guidelines.