A Feasibility Trial of Managing Cancer and Living Meaningfully (CALM) in Patients with Newly Diagnosed and Recurrent Advanced Ovarian Cancer

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1. ABSTRACT.

Ovarian cancer is a common and fatal disease, ranking seventh in prevalence and eighth in fatality worldwide, with a 5-year survival rate of 44% in Canada. Traumatic stress symptoms (TSS) may be prevalent in those affected, particularly at the time of diagnosis and recurrence, because of the perceived threat to life, invasive surgical procedures and distressing physical burden of the disease and treatment. However, proactive psychotherapeutic care is not routinely implemented as standard of care in this population. The proposed multi-method study is designed to determine the feasibility and acceptability of implementing a brief evidence-based psychotherapeutic intervention, Managing Cancer And Living Meaningfully (CALM), at the time of diagnosis and recurrence of ovarian cancer. CALM addresses four broad domains: symptom management, changes in self and relationships, meaning in life, and hopes and fears about the future. While CALM has demonstrated effectiveness in reducing depression, death anxiety and increasing preparation for end of life among patients with advanced cancer later in the illness trajectory, its feasibility and effectiveness in addressing TSS soon after a diagnosis of advanced cancer has not previously been established. Findings of this study could inform the potential development of a larger randomized effectiveness trial.

2. BACKGROUND.

2.1 Clinical Characteristics and Progression of Adult Ovarian Cancer. Globally, ovarian cancer (OC) ranks seventh in prevalence and eighth in fatality worldwide, affecting 1% of individuals. In Canada, the 5-year survival rate stands at 44% (Canadian Cancer Society, 2016). Among women, OC is ranked as the fourth fatal disease (Chandra et al., 2019). If identified in the early, localized stages (stage I or II), a combination of cytoreductive surgery and conventional chemotherapy leads to cure OC in 70-90% of patients. However, only 20% of patients are diagnosed at early-stages (Chandra et al., 2019). Patients with OC are often diagnosed late, primarily due to the asymptomatic nature of early-stage disease (Carlson, 1994; Jayson et al., 2014). At the time of diagnosis, advanced-stage disease (i.e., stage III or stage IV) is already present in 75% of cases (Colombo et al., 2006), which is characterized by a high risk for recurrence (Gonçalves, 2011) and poor prognosis (Dinkelspiel et al., 2015).

The initial treatment of OC involves surgery (Armstrong et al., 2022) that may include thorough examination of the peritoneal cavity, total abdominal hysterectomy, omentectomy and bilateral salpingo-oophorectomy (Jayson et al., 2014; Lederman et al., 2013). Following surgical procedures, patients with semi-resection, advanced-stage cancer, or early-stage illness with high risk of recurrence typically also require chemotherapy (Jayson et al., 2014; Lederman et al., 2013). The various procedures and treatment modalities can be distressing and are highly intrusive.

2.2 Prevalence and Severity of Traumatic Stress in Ovarian Cancer. Traumatic stress manifests as a heightened and unsettled emotional state that can emerge following the exposure to traumatic events, defined in the DSM-5 as “circumstances involving actual or potential threats to life” (American Psychiatry, 2013). In oncology, the diagnosis, progression, or recurrence of life-threatening cancers are inevitably

experienced as traumatic events of this kind (Cordova et al., 2017) under this definition. The DSM-5 categorizes TSS into four clusters: 1) re-experiencing symptoms, which involve intense distress triggered by internal or external reminders of the trauma; 2) deliberate efforts to avoid such reminders; 3) alterations in cognition and mood; and 4) arousal symptoms, characterized by excessive irritability and anger, hypervigilance, exaggerated startle response, reckless or destructive behaviours, reduced concentration, and disturbed sleep.

Specific constellation of TSS experienced within the initial month following the exposure to a traumatic event may meet criteria for acute stress disorder (ASD) or, if symptoms persist for over a month, post-traumatic stress disorder (PTSD; American Psychiatry, 2013; Spiegel et al., 2005). Research shows that approximately 80% of individuals diagnosed with ASD, eventually develop PTSD (Bryant, 2003). PTSD is a common manifestation of psychological distress among cancer patient populations (Andrykowski et al., 1998; Andrykowski & Cordova, 1998; Cordova et al., 1995; Goncalves et al., 2011; Guglietti et al., 2010; Kangas et al., 2002; Kangas et al., 2005; Roberts et al., 2019; Rodin et al., 2013).

ASD and PTSD have a substantial impact on affected individuals, including increased risk for suicide (Gradus et al., 2010) and psychological disorders (Mehnert & Koch, 2006), shifts in personality, issues with substance abuse (Brady et al., 2004), and impaired quality of life (QoL; Holbrook, et al., 2005; Lefebvre et al., 2020). It may also be associated with the development of a range of health conditions, including cardiovascular (Carmassi et al., 2020), metabolic (Farr et al., 2014) and musculoskeletal disorders (Wachen et al., 2013). While traumatic stress has been widely studied in other trauma-exposed populations, it is a highly understudied phenomenon in oncology (Vujanovic & Bernstein, 2011).

We investigated the prevalence and severity of TSS in a large longitudinal study involving more than 350 patients with newly diagnosed or recently relapsed acute leukemia. We found that over 30% of participants reported TSS that met the criteria for threshold or subthreshold ASD (Rodin et al., 2013) and that these symptoms persisted or recurred in more than half of the participants during the three-month follow-up period (Rodin et al., 2020). Notably, these rates exceeded those reported in other trauma-exposed groups, including survivors of motor vehicle accidents (Harvey et al., 1998), physical assault (Harvey et al., 1998), or adult congenital heart disease (Deng et al., 2016). Even higher rates of TSS are observed in the primary family caregivers of patients, most commonly parents, spouses, or adult children. In a parallel CIHR-funded research project conducted by our team at the Princess Margaret Cancer Centre (#438301; Co-PIs Rodin & Jibb; CTO/OCREB Study ID:2104), preliminary results indicate that an alarming proportion of parents of children (64%) and family caregivers of adults diagnosed with this disease (68%) reported clinically significant TSS (Malfitano et al., TBD), proportions that are more than twice as high as what is typically seen in other individuals who have been exposed to trauma.

Despite emerging evidence for the commonality and adverse impact of TSS among individuals diagnosed with cancer and their caregivers, particularly at the time of diagnosis or recurrence of advanced cancer, there has been little research investigating the feasibility and acceptability of implementing psychotherapeutic

interventions addressing TSS at these times. Research suggests that addressing PTSD symptoms proactively and shortly after the exposure to a traumatic event (i.e., new diagnosis/recurrence) can reduce the likelihood of developing PTSD (Bryant et al.,1998; Harvey et al., 2003; Foa et al., 1995). Although it has been found that cognitive-behavioural therapy (CBT) may mitigate or prevent the onset of PTSD among patients with early-stage cancers (Bryant et al., 1998; Harvey et al., 2003; Foa et al., 1995), CBT has been shown to be ineffective in treating distress in patients with advanced cancer (Serfaty et al., 2019). Additionally, common obstacles to offering psychosocial support include limited availability of evidence-based interventions and lack of trained healthcare providers (Powel et al., 1998; Stead et al., 2001).

2.3 CALM. Over the past 15 years, our team has developed, refined, and tested a brief, manualized, individual and couple-based psychotherapeutic intervention for patients living with advanced cancer and their primary caregivers called Managing Cancer and Living Meaningfully (CALM; Lo et al., 2013). CALM is a brief supportive-expressive therapy consisting of 3-6 sessions of 30-60 minutes delivered over the course of 3-6 months. This tailored therapy is focused on the most common challenges and concerns facing individuals living with advanced cancer. These four broad content domains are: 1) symptom management and communication with healthcare providers; 2) changes in self and in relationships with close others; 3) sense of meaning and purpose in life; and 4) hopes and fears about the future and mortality (Rodin & Hales, 2021). The attention to each of these domains varies based on the specific concerns most pertinent to each patient. The aim is to offer patients and caregivers reflective space and a supportive environment to reflect on and process the various practical and profound aspects of their life while facing advanced illness (Lo et al., 2016).

A large body of research, including large randomized controlled trials (RCTs), conducted by our team and others, has demonstrated that CALM is a feasible and highly beneficial intervention for this population (Caruso et al., 2020; Lo et al., 2016; Mehnert et al., 2020; Nissim et al., 2011, Rodin et al., 2018). In a large phase III RCT of CALM plus usual care versus usual care alone in 305 adult patients with advanced cancer, we demonstrated that CALM is effective in reducing depressive symptoms at 3 and 6 months and increasing preparation for the end-of-life at 6 months (Rodin et al., 2018). With this promising evidence, we now propose to test the feasibility, and acceptability CALM adapted to address TSS early in the illness trajectory and as part of routine care among individuals with newly diagnosed or recently recurred advanced OC.

2.4 CALM National Program. We received a generous donation from the Weston Family Foundation to develop a sustainable National Program to integrate CALM into standard care of advanced cancer in 10 comprehensive cancer centres across Canada and to establish CALM as a psychotherapeutic intervention available to support Canadians facing this life-threatening condition. This national program will be implemented in 3 consecutive phases, each lasting 18 months. The Cancer Experience Program will coordinate the implementation of this program, together with

the Global Institute of Psychosocial, Palliative and End-of-Life Care (GIPPEC), both based at Princess Margaret (PM) and both directed by Dr. Rodin.

During Phase 1, we will design, implement, and test procedures at PM, in collaboration with tumour site leaders and champions at our centre. During Phase 2, we will train CALM clinicians and supervisors in 5 additional cancer centres in British Columbia (British Columbia Cancer Agency), Alberta (Tom Baker Cancer Centre), Quebec (University de Montreal Hospital Research Centre), Manitoba (Cancer Care Manitoba), and Newfoundland and implement procedures tested at PM. During Phase 2, we will also identify 4 additional Canadian cancer centres. During Phase 3, we will train CALM clinicians and supervisors and implement procedures at these additional 4 cancer centres.

By the end of phase 3, we expect that local CALM clinics at each participating centre will have reached a self-sustainable ecosystem with established pathways for referrals and local CALM therapists and supervisors. Our team at PM will continue to provide training opportunities, support to supervisors and centres, national collaborations, and academic support in continuity through the support of GIPPEC.

We are strategically linking the CALM National program's quality improvement study with this study. This deliberate integration means that participants will only be required to complete study measures once to significantly reduce the overall burden on patients.

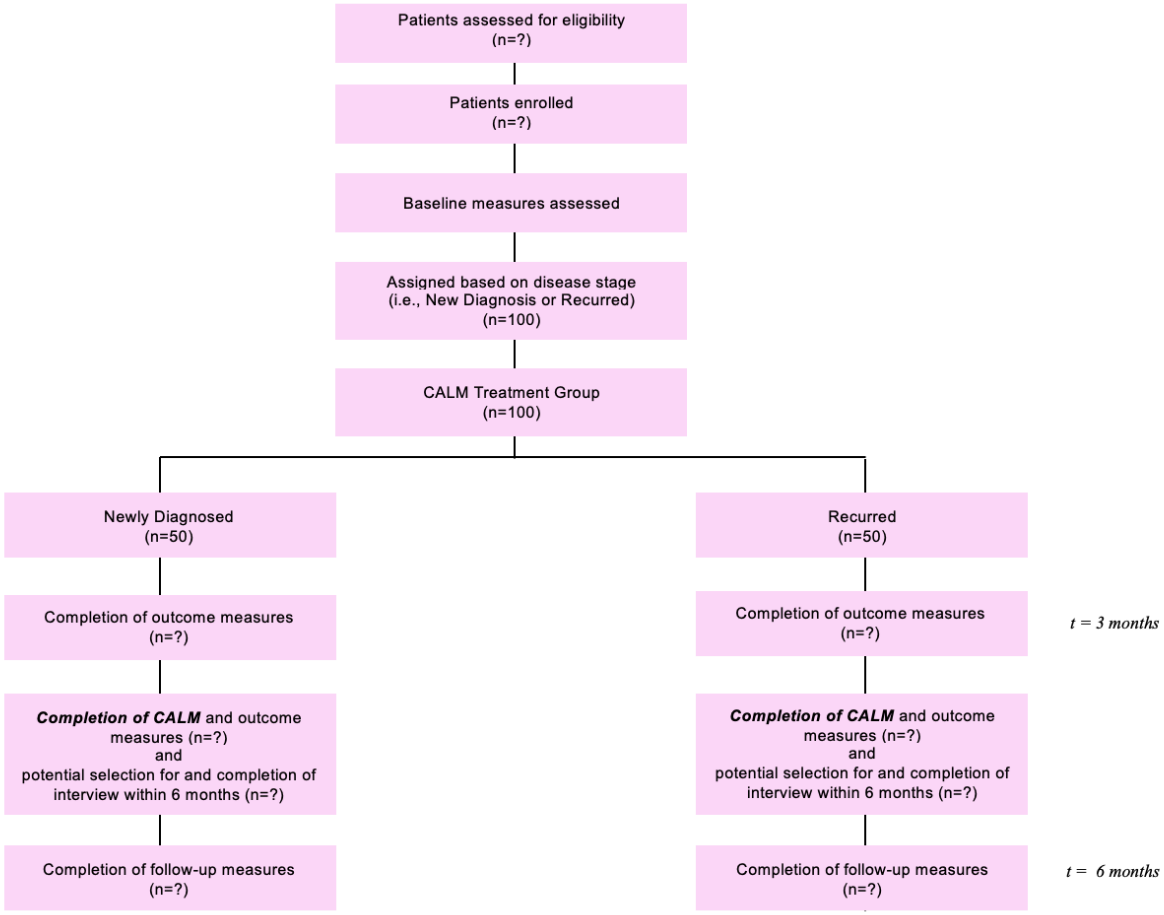
3. STUDY RATIONALE AND OBJECTIVES.

3.1 Study Rationale. In light of the frequency and impact of TSS in patients with advanced cancer, the complex challenges faced by patients living with advanced OC, and the lack of proactive, specialized, and evidence-based psychosocial support, we aim to evaluate the feasibility and acceptability of the proactive delivery of CALM in reducing TSS in patients with newly diagnosed or recently recurred advanced ovarian cancer.

3.2 Objectives. To conduct a multi-method, single-arm phase II trial of the early and proactive delivery of the CALM intervention to patients with advanced OC. The primary objectives are to assess in this sample: **(1)** the feasibility and acceptability of implementing CALM for patients with newly diagnosed or recently recurred advanced OC; **(2)** the prevalence and correlates of TSS at baseline in patients with newly diagnosed or recently recurred advanced OC.

4. THE PROPOSED STUDY.

4.1 Design. This study will involve a multi-method, single-arm, phase II trial, enrolling a total of 100 OC patients (50 newly diagnosed and 50 recently recurred), with measurements at baseline, 3 months and 6 months. Participants who declined to participate in the intervention will be invited to share their reasons for opting out, contributing valuable insights to our records. A subset of purposefully sampled participants will also complete qualitative interviews following the completion of outcome measures at 6 months.



4.2 Setting. The single-arm pilot trial will be conducted at Princess Margaret Cancer Centre (PM). The Princess Margaret Cancer Centre is the largest cancer centre in Canada and one of the largest in the world. PM, based at the University Health Network, stands as the largest and one of the world's top five comprehensive cancer programs. Located in the city of Toronto, Canada's largest and most diverse city, patients come from a wide range of backgrounds. This study will be focused within the Gynecologic Oncology Clinic. PM is an ideal setting for this non-randomized pilot trial, given its dedicated OC program that serves a large number of both newly diagnosed and recurrent OC patients.

4.3 Inclusion and Exclusion Criteria. **Inclusion criteria**: **(i)** new diagnosis or recurrence of stage III or stage IV OC; **(ii)** age ≥18 years **(iii)** able to complete outcome measures and engage in CALM in English. **Exclusion criteria**: **(i)** evidence of cognitive impairment indicated in the medical record, communicated by the OC clinic team, or determined by research staff at recruitment; **(ii)** receiving psychological or psychiatric counseling from the Department of Supportive Care at PM at the time of recruitment.

4.4 Feasibility and Acceptability Outcome Criteria: Predefined feasibility criteria are outlined as follows: (i) accrual of 50 newly diagnosed and 50 recurred patients

over 12 months; **(ii)** ≥64% of CALM patients (i.e., 32/50 newly diagnosed and 32/50 recurred) complete at least 3 sessions over 6 months; **(iii)** ≥64% complete outcome measures ≥50% of the time; **(iv)** >50% score >14 on the Clinical Evaluation Questionnaire (CEQ)—CALM (*Section 5.1*).

4.5 Study Procedures. 50 patients with newly diagnosed stage III or IV OC and 50 with recently recurred OC will be recruited from the PM outpatient OC clinic. The recruitment and follow-up process will be as follows:

1. Patients with newly diagnosed or recently recurred with stage III or IV OC will be identified by a member of the patient's circle of care, who will securely communicate this information to the research team. In addition, our research staff will access to patient lists/rosters and medical charts (paper or electronic), to identify eligible patients or to verify the patient's medical eligibility. For individuals who are ineligible, reason for ineligibility will be documented in the study's research records;

2. A member of the patient's circle of care will introduce the study to eligible patients within 6 months of a new diagnosis or recurrence and ask permission for the research team to approach. Those who do not wish to be approached for research will not be contacted by the research team. Members of the patients circle of care may also provide the patient with an introductory letter which includes additional information about the study as well as contact information. Patients who agree to be approached by the research team, will be approached in person, over the telephone or MS Teams (see OC PIIT+Recruitment+script, section 1: In-person/ Over the Telephone/ MS Teams script) by a member of the research team who will provide the patient with a brief introduction to the study. If the patient expresses interest in the study, following the brief introduction, a member of the research team will provide the patient with a consent form via their preferred method (email, mail or in-person) and proceed with the consent discussion, which can happen in-person, over the telephone or via MS Teams. Patients will be provided with ample time to review the consent form and ask questions;

3. Consenting patients will be asked to complete baseline questionnaires and will be referred to a CALM therapist who will contact patients as soon as possible. Questionnaires will take approximately 20 minutes to complete. Consent forms and study questionnaires will be administered through REDCap or any other future equivalent UHN-approved online software that ensures privacy compliance at the government, regulatory, and institutional levels. Upon patients request, paper copies of the consent forms or study questionnaires can also be provided to patients in-person or mailed to their preferred address. Consent forms and study questionnaires can also be provided through secure UHN file portal.

4. For individuals who decline to be approached by the research team or decline participation in the study, the study team will document the reason for refusal, if patients feel comfortable sharing it. This is very important data to evaluate the optimal timing of delivery of the intervention as well as other barriers to access

specialized psychotherapeutic services which is one of the main objectives of this study. This data will be recorded in a member of the research team's source notes;

5. Study participants will be asked to complete a similar questionnaire package at 3 and 6 months. If the study participant does not complete and return the questionnaires within 1 week, they may receive up to 2 reminder in-person visits or phone calls from the research staff. Patients who cannot be reached will be categorized as lost to follow-up for that specific assessment (*note*: patients may be re-approached for subsequent assessments);

   After completion of the 6-month follow-up questionnaire or withdrawal from the study, a subset of participants will be purposefully sampled and invited to participate in one or more qualitative interviews (*please refer to section 5.5.2)*. Reason for withdrawal will be recorded for all participants if they are comfortable providing this information to the research team.

4.6 Non-randomized Trial Intervention.

4.6.1 CALM. Managing Cancer and Living Meaningfully (CALM) is a brief, semi-structured, individualized psychotherapeutic intervention developed by Dr. Gary Rodin and colleagues at the Princess Margaret Cancer Centre. CALM is structured to offer patients a framework and a reflective space to explore the practical and profound challenges that often accompany an advanced cancer diagnosis (Rodin & Hales, 2021). CALM focuses on incorporating four domains: 1) symptom management and communication with healthcare providers; 2) changes in self and in relationships with close others; 3) sense of meaning and purpose in life; and 4) hopes and fears about the future and mortality (Lo et al., 2013; Rodin et al., 2018). CALM therapy consists of 3-6 sessions that are approximately 30-60 minutes in length over the course of 3-6 months (Rodin et al., 2018; Nissim et al., 2011). Sessions will be conducted over the telephone, through MS Teams, or in person at PM, based on the preference of the patient and availability of the therapist. Primary caregivers will be invited to attend one or more sessions. Patients and primary caregivers may be asked for permission to video-record their therapy sessions for research and educational purposes. In this instance, participants will be asked to sign a separate consent form (see "consent to video-record").

4.7 Treatment Integrity. The fidelity of the CALM intervention will be upheld by following the CALM treatment manual (Rodin & Hales, 2021). Supervision meetings will be offered weekly or bi-weekly and will be led by Drs. G. Rodin and C. Malfitano and treatment integrity will be assessed with CALM Treatment Integrity Measure (CTIM; Rodin & Hales, 2021). Therapists will be rated using a treatment integrity scale (Koranyi et al., 2020). Based on the treatment integrity scale, these assessments will cover various aspects of the intervention. Feedback resulting from these evaluations will be shared with the therapist(s) for the purpose of enhancing any competencies that are found to be below the expected standards. These procedures align with the recommendations made by other experts in the field (Perepletchikova & Kazdin, 2005; Barber et al., 2007).

5. STUDY MEASURES, DATA COLLECTION AND ANALYSIS.

5.1 Study Measures. The primary outcome will be TSS which will be assessed using the **Stanford Acute Stress Reaction Questionnaire** (**SASRQ;** Cardena et al., 2000), a self-reported DSM-IV correspondent scale to measure a range of symptoms associated with Acute Stress Disorder (ASD), encompassing dissociation, trauma re-experiencing, avoidance behaviors, anxiety, hyperarousal, and functional impairment. The SASRQ consists of 30-items utilizing a 6-point scale that ranges from 0=*not experienced* to 4=*very often experienced.* Demonstrating robust psychometric properties, including strong test-retest reliability (Cardena et al., 1996) and consistent evidence of predictive, construct, discriminant, and convergent validity across varied populations (Cardena et al., 2000; Cardena & Spiegel, 1993; Freinkel et al., 1994), the SASRQ serves as a reliable and valid tool for assessment. This questionnaire will be administered at all timepoints.

Patient's thoughts, feelings and experiences with romantic partners will be assessed through the **Modified Experiences in Close Relationships (ECR-M-16)** measure (Lo et al., 2009). The ECR-M-16 is a validated measure with 16-items, has been thoughtfully adapted to be less time-consuming and alleviate any potential burden for patients who may be physically unwell (Lo et al., 2009). This questionnaire will be administered at baseline.

The prevalence, frequency, severity, intensity and emotional impact related to typical physical and psychological symptoms experienced by cancer patients participating in the CALM intervention. The **Condensed Memorial Symptom Assessment Scale (CMSAS)**. The CMSAS stands as a straightforward and validated self-report evaluation tool, comprising 14 items. It effectively gauges various aspects such as energy level, dry mouth, appetite, weight loss, pain, nausea, drowsiness etc. These facets are organized into three subscales: physical, psychological and symptom distress (Chang et al., 2004). This questionnaire will be administered at all timepoints.

Depression will be measured using the **Patient Health Questionnaire (PHQ-9)**, a diagnostic tool used in primary care settings to establish criteria-based diagnoses for depression (Kroenke et al., 2001). PHQ-9 is a 9-tem, self-reported questionnaire which consists of the 9 depression criteria which is highlighted within the DSM-IV (Grant et al., 2009). PHQ-9 is particularly favoured due to its concise structure, which efficiently identifies the presence of depressive disorders and is also able to rate the severity of depressive symptoms (Kroenke et al., 2001). This questionnaire will be administered at all timepoints.

Death anxiety will also be assessed using the **Death and Dying Distress Scale (DADDS)**, a tool used to evaluate the distress caused by a patients thoughts on death and dying over the previous two weeks (Lo et al., 2011). DADDS is a 15-items questionnaire with the aims of alleviating the fear of death and fostering psychological development (Nissim et al., 2011; Shapiro et al., 2021).The validity of DADDS has been rigorously established, with factor analysis demonstrating distress related to two factors: Finitude and Dying (Shapiro et al., 2021). This questionnaire will be administered at all timepoints.

Furthermore, participants will also complete the **Clinical Evaluation Questionnaire (CEQ)—CALM**, a 7-item validated questionnaire, created by our research team to assess the perceived benefit of interactions with health care providers in domains relevant to advanced cancer (De Vries et al., 2022). This questionnaire will be administered at timepoint 1 and timepoint 2 only.

5.2 Data Collection. Following the consent process, patients will be asked their preferred method for completing the study measures (i.e., online, paper copy, or over the telephone):

i. **[If Online]** The participant will be informed that they will receive a unique, automatic, personalized access link to the online survey directly from RedCap. The unique access link may also be provided to participants by email, from the study coordinator's UHN email account, upon participants' explicit request.
ii. **[If Paper Copy]** The research team member will confirm participant's mailing address; participant will be informed that they will receive the questionnaire package via mail (or in person at PM if/when permitted). They will be instructed to send back the completed questionnaires using a return envelope provided in the package;
iii. **[If Over Telephone/MS Teams]** The participant will be asked to determine a date/time for which the study coordinator can call them to complete the questionnaires via the telephone or online through MS Teams (or a future, UHN-approved software). The participant will have the option for a blank copy of the questionnaire package or a handout containing the standardized answers for each questionnaire (*see "patient's scales handout"*) to be emailed to them as a password-protected pdf file so they can follow along while completing the measures over the telephone.

5.2.1 Online Data Collection. If a participant wishes to complete their study measures online, this will be done using the secure REDCap online, **external instance** platform (https://external.redcap.uhn.ca/). The REDCap database is stored on secure UHN servers located in Toronto, Canada and are compliant with all UHN Privacy requirements. Access to REDCap will be restricted to authorized users. A copy of the database may be downloaded periodically and stored in a password-protected file on a secure UHN network server or on encrypted, backed-up, and securely stored hard-drives. No personal identifiers will be collected or stored on the external REDCap database. Personal identifiers, such as demographic information and medical information, will be collected over the phone directly from patients or collected from patient health records. This information will be stored either on a password-protected file (e.g., Excel spreadsheet) on a secure UHN network server, on encrypted, backed-up, and securely stored hard-drives, and/or on an **internal** REDCap instance platform (https://internal.redcap.uhn.ca/).

5.2.2 Video Data Collection. Participants will be asked for consent to video-record their therapy sessions or qualitative interviews for training and educational purposes.

Participants will be informed that consenting to this component of the study is optional and that refusal will not impact their care or participation in the study. Please see "Optional Video Recording Consent Form".

5.3 Data Management. All data will be stored on secure servers and automatically and regularly backed up. Paper copies of the study documents will be stored in locked cabinets in locked offices at PM. Hardcopy documentation will be manually entered into databases by members of the reach team and double-checked for accuracy. Upon request, a lay summary of the study results will be shared with the patient after the entire study is completed.

5.4 Proposed Sample Size, Recruitment.

5.4.1 Proposal Analysis. The primary objective of this single-arm pilot trial is to assess the feasibility and accessibility of CALM at the time points of diagnosis and recurrence of advanced OC. We plan on recruiting 50 participants who are newly diagnosed with OC and 50 who have recurred. For the qualitative arm of the study, we plan on recruiting 15-20 participants or until theme saturation is achieved.

5.4.2 Planned Recruitment Rate and Recruitment Period. The recruitment strategy is designed to approach 100 patients (50 who are newly diagnosed and 50 patients with recurred OC). The accrual 30% of newly diagnosed and recurred patients approached over a 12 month period, beginning from January 2024.

5.5 Analysis

5.5.1 Quantitative Data Analysis. R software will be used for all analyses. Descriptive analyses (means and standard deviations, n and %) will be conducted to describe the sample characteristics and to report mean total and subscale scores and standard deviations at baseline and at each follow-up for the trial measures (PCL-5, CMSAS, PHQ-9, DADDS, CEQ).

To evaluate the feasibility and acceptability of the CALM intervention, we will conduct the following descriptive analyses in accordance with the criteria outlined in section *4.4 Feasibility and Acceptability Outcome Criteria*: (i) accrual 30% of newly diagnosed and recurred patients approached over a 12-month recruitment period. We will conduct frequency analyses to identify the percentages of newly diagnosed and recurred patient participants who (ii) complete ≥64% of CALM sessions, (iii) complete ≥64% of the outcome measures ≥50% of the time, and (iv) >50% score $\underline{\geq}$14 on the CEQ.

5.5.2 Qualitative Data Collection and Analysis. In order to gain a deeper understanding of the willingness or reluctance of patients recently diagnosed or experiencing a recurrence to engage in the CALM intervention, we will conduct qualitative interviews with a select group of participants. This subset will include participants who were approached for the study and consented to participate in the study. Patients expressing interest in participating in this aspect of the study will be contacted to initiate a separate consent process, which will adhere to the procedures outlined in *section 4.5*. The interviews can take place either in-person at PM or

conducted remotely via MS Teams or telephone, depending on the preference of the patient. Audio recordings will capture the qualitative interviews, and, with participant consent, video recordings may also be made for research and training objectives.

The aims of these interviews will be to understand the patient's experience of the intervention and reasons for accepting or refusing to participate in psychosocial support at the two pivotal timepoints (new diagnosis and recurrence). We will employ a purposeful sampling approach (Palinkas et al., 2013) to select participants from both newly diagnosed and recurrent patient groups, considering the prevalence of acceptance across both timepoints. This methodology entails the recruitment of participants with prior exposure to CALM therapy, who are willing and available to articulate, express and reflect upon their experiences and opinions (Bernard, 2002; Spradley, 1979). Appropriate newly diagnosed and recurred participants who agreed to partake in the intervention will be invited to a semi-structured interviews to discuss the journey with their illness, psychosocial support they received and their experience with the intervention based on their disease state.

Qualitative interview study participants will be provided with sufficient interview time and thoughtful probes to provide patients with the opportunity to expand on their comments and enable the interviewer to seek clarification, encouraging participants to deeply contemplate these subjects. The interview guide (*please refer to the attached interview guide*) will undergo frequent modifications, such as adapting to emerging themes during each interview or for delving deeper into themes identified by previous participants. The decision to conduct follow-up interviews with the same study participants will rely on our ongoing comparative analysis approach and the participants willingness to partake in additional interviews. As participants engage in interviews at various timepoints, the insights gleaned from their initial interviews will be incorporated into subsequent interviews to grasp how patient perceptions and experiences evolve over time. The analysis of qualitative interviews will employ the qualitative description method, adapted to entail low interference (Sandelowski, 2000). Grounded in a pragmatic worldview, this methodology emphasizes the centrality of human experiences as the fundamental approach for knowledge construction and understanding the world, steering away from reliance on absolute truths (Allemang et al., 2021; Hildebrand, 2011). Instead, it focuses on uncovering the who, what and where dimensions of experiences (Sandelowski, 2000). This approach proves particularly valuable when a need arises for straightforward descriptions of phenomena (Sandelowski, 2000). Interviews will be conducted within 6 months following the completion of the intervention. The semi-structured interviews will remain flexible and undergo ongoing improvements guided by the feedback and insights provided by patients, the researchers and the ovarian cancer clinical team. Interview recordings will undergo electronic transcription, followed by accuracy checks conducted by MG. The transcriptions, along with fieldnotes, will then be imported into NVivo12.0 software for the purpose of analysis. Data analysis will begin soon after the initial interview is transcribed, allowing for insights and themes to be identified in the early interviews to influence the analysis of subsequent interviews (Sandelowski, 2000). Observed differences in coding interpretations will be addressed through discussion within our study team, and these discussions will be held frequently during data analysis review meetings.

6. ETHICAL CONSIDERATIONS.

6.1 Informed Consent. Prior to their involvement, participants will be required to give informed consent. The consent forms will present the study and its goals using lay language. It will also detail the potential advantages and risks for participants, the freedom to withdraw from the study at any point without any impact on their clinical care. Furthermore, the forms will explain the measures in place to ensure the confidentiality of collected data. Each patient will provide a signed consent form, which will be witnessed. Additionally, separate consent will be sought from those who choose to participate in qualitative interviews.

6.2 Privacy and Confidentiality. All participants will be assigned a unique subject identification number (ID) and all records will be stored by this number. All data will be coded by ID, and patients' identifying information (specifically names, addresses, contact information, site-specific medical record numbers) will not appear on any study related documents or electronic forms (e.g. measures), with the exception of the paper copies of the consent forms by means of the participants' signature, the master lists linking participants' names to ID numbers, and the databases used to track and contact study participants. All study-related documents and electronic forms will be accessible only to members of the research team at PM. The option of storing digital data (video-recordings and any other study-related document, including those listed above) into the secure servers will be made available through secure remote access, secure file portal, or stored into digital storage units (e.g. external drives, USB keys, etc.) and securely transported. Research data collected at PM through the online database will be downloaded into PM secure servers periodically. Research data as well as all collected video-recordings will be identified by ID number only and, when not in active use, will be safely stored in a password-protected database on secure network servers at PM or encrypted, backed-up and securely stored hard-drives that are also password-protected. All research computers and any other data storage devices at PM have also been encrypted for added security. All paper copies of documents will be consolidated in standardized folders and stored in locked cabinets located in locked offices at PM. Data that is published will in no way identify the individual participant or disclose their identity. Participant identity information will primarily be used to confirm study inclusion/exclusion eligibility criteria (e.g., confirm ovarian diagnosis), to contact the participant with regard to assessment mailings and/or scheduling appointments for the qualitative interviews. Any information related to recruitment will be securely stored and subsequently destroyed following completion of recruitment and data consolidation and verification. All paper-copy data will be securely stored and destroyed 10 years after study completion (or for 7 years if it does not contain personal health information). 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 the participant's ID and also securely stored in secure servers at PM or in locked office filing cabinets in locked research offices at PM. Audio-files and transcripts will be securely stored and destroyed 10 years after study completion. De-identified transcripts (i.e. with names, identifying

information, and site-specific medical record numbers deleted from the final document) will be shared at PM for data analysis. If printed, hard copies of the transcripts will be filed in the patient's study chart.

6.3 Risks and Mitigation Strategies. Consent forms will describe the study and its objectives in lay terms, outline potential benefits/risks to participants, indicate that participants are free to withdraw at any time without adversely affecting their clinical care, and outline what safeguards will be taken to maintain confidentiality of data. Participants who withdraw consent will be asked which parts of the study they wish to withdraw from. Specifically, participants can choose to withdraw at any time from: 1) completion of follow-up questionnaires; 2) completion of further data collection, including chart review; 3) qualitative interviews; or 4) all study activities (all of the above). These study-related activities will then be discontinued immediately following participant withdrawal. If a patient allows us to document chart review information following withdrawal and/or completion of study activities, this will be documented. If a patient allows us to contact them for the qualitative interviews following withdrawal and/or completion of other study activities, this will be documented and a separate qualitative consent process will follow. Should a patient report information related to a health concern or risk (including suicidal ideation by answering “yes” to question #9a in the PHQ-9) while completing the questionnaires or during the interview, the research team will: (i) initiate a risk assessment procedure (and any related action that must follow) if the research staff is a member of a profession that requires this response (e.g. social work or nursing); (ii) contact the psychiatrist on call for an urgent consultation; iii) immediately inform the PIs at each respective site; and (iv) implement any decision communicated by medical personnel and the PIs. Any action(s) suggested by medical personnel the PIs will be documented in the participants’ research folders.

7. ENVIRONMENT, EXPERTISE, AND RESOURCES.

7.1 Research Environment. The Gynecologic Oncology Clinic within PM has recently begun a comprehensive OC program aimed at streamlining the patient referral process, ensuring that every referral is assessed and scheduled for a clinic appointment within 7 business days. The proposed research initiative is being undertaken within this program and is extremely well-positioned for its success, given the well-developed research infrastructure and administrative supports from the PM institution that is in place (e.g., dedicated study space, research support staff, access to clinical research support units, and data analysis and knowledge translation [KT] expertise). Our team’s affiliations with the University of Toronto (UT) also provide us with further access to study space, statistical and administrative support. Moreover, this research will be conducted with the early and ongoing engagement of the OC clinical team and other stakeholders and will remain embedded on the research team to support the ongoing conduct of the study and interpretation and dissemination of the data.

7.2 Role of Research Team. Principal Investigator: Gary Rodin MD: Senior Scientist and Director of the Global Institute of Psychosocial, Palliative and End-of-

Life Care (GIPPEC) and the Cancer Experience Program; internationally recognized for his research on psychological disturbances and psychotherapeutic interventions in patients with advanced disease; **Co-Principal Investigator: Stephanie L'Heureux MD, PhD:** Drug Development Program**,** Division of Medical Oncology & Hematology – Gynecology; Gynecology Site Lead Westaway Chair in Ovarian Cancer Research; Associate Professor, University of Toronto; **Graduate Student Researcher: Megan A. George BSc:** Medical Science Master's Student, Institute of Medical Science (IMS), University of Toronto, Faculty of Medicine, Princess Margaret Cancer Centre; **CALM Therapists**: **Carmine Malfitano PhD, MSW:** Clinician Specialist, Princess Margaret; Social Worker, The Hospital for Sick Children; Research Associate, Global Institute of Psychosocial, Palliative and End-of-Life Care; experience with research coordination in psychosocial oncology and palliative care**; Argin Malakian RN, MN**; **Kate Hunt**; **Laura Foran**; **Maya Stern**; **Elizaveta Klekovkina**. **Collaborators**: **Kenneth Mah, PhD, CPsych:** Scientific Associate, Supportive Care, PM**;** expertise in trial design, psychosocial oncology, statistical methodology and data analysis. Role: trial-design and implementation consultation, data analysis and interpretation. **Referring Physicians**: **(i)** Medical Oncology Team – **Amit Oza**; **Robert Grant**; **Neesha Dhani**; **Stephanie L'Heureux**; **(ii)** Gynecology Oncology Team – **Lauren Philip**; **Genevieve Bouchard**; **Taymaa May**; **Sarah Ferguson**; **Marcus Bernardini**; **Stephane Laframboise**; **Liat Hogen**; **Rachel Kim**.

7.3 Trial Steering Committee and Data Safety and Monitoring Committee. The trial steering committee, jointly led by Dr. Gary Rodin, Dr. Carmine Malfitano, and Dr. Stephanie L'Heureux, will convene on a quarterly basis, and as required. Their role will involve evaluation of patient safety, data integrity and the advancement of the trial. Further, they will conduct weekly research meetings with the team to assess the study's advancement, gather participant insights, and address any adverse events.

8. KNOWLEDGE TRANSLATION (KT) AND EXPECTED IMPACT.

This study represents a continuing endeavor by our team to create a holistic and timely psychosocial support system for individuals facing life-threatening and advanced cancer. Our previous work has already illuminated the widespread necessity for psychotherapeutic interventions tailored to these specific patient populations. Interventions such as CALM are crucial in aiding individuals in the effective management of their symptoms and enhancing their overall quality of life. At present, our knowledge through the single-arm, phase II pilot trial, we will gain insights into the efficacy of CALM in mediating traumatic stress as well as the optimal timing of intervention. Knowledge translation (KT) objectives aims to leverage this fundamental knowledge, propelling the dissemination of early CALM intervention for patients with advanced cancer and ultimately integrating it as a standard component of routine care. The rigorous nature of this study will yield insights that deeply enhance our comprehension of the patient experience at two critical junctures within the trajectory of the ovarian cancer. This understanding will, in turn, facilitate the refinement of the CALM intervention and reform a potential large effectiveness trial, as part of the broader National CALM project.

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(NOTE: Our research team's publications are distinctly bolded.)

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