



BMJ Open Brief, manualised and semistructured individual psychotherapy programme for patients with advanced cancer in Japan: study protocol for Managing Cancer and Living Meaningfully (CALM) phase 2 trial

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To cite: Miyamoto S, Yamazaki T, Shimizu K, *et al.* Brief, manualised and semistructured individual psychotherapy programme for patients with advanced cancer in Japan: study protocol for Managing Cancer and Living Meaningfully (CALM) phase 2 trial. *BMJ Open* 2022;**12**:e056136. doi:10.1136/bmjopen-2021-056136

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-056136>).

Received 06 August 2021
Accepted 09 February 2022



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ABSTRACT

Introduction Managing Cancer and Living Meaningfully (CALM) is a novel, brief and manualised psychotherapeutic intervention intended to treat and prevent depression and end-of-life distress in patients with advanced cancer. This phase 2 trial aims to assess the feasibility and preliminary efficacy of CALM in Japanese patients with cancer.

Methods and analysis This study is a single-arm clinical trial. All patients involved in the study are ≥18 years of age, have been diagnosed with advanced or metastatic solid-tumour cancer, and their expected survival is at least 6 months. CALM comprises three to six individual therapy sessions, each lasting approximately 45–60 min, provided over 3–6 months. The participants will be asked to complete questionnaires at baseline (t0), 3 months (t1) and 6 months (t2). The primary outcomes are rates of completion of the intervention and of the outcome measures and improvement of depressive symptoms measured using the Patient Health Questionnaire-9 between t0 and t2. The criteria for the successful rate of completion is that at least 70% participants who participate in at least three sessions will complete measures at t2. The secondary outcomes are the improvement in scores on: (1) the Quality of Life at the End of Life-Cancer Scale, (2) the Experiences in Close Relationships scale, (3) the Death and Dying Distress Scale and (4) the Clinical Evaluation Questionnaire.

Ethics and dissemination This study was approved by the Research Ethics Committee of The University of Tokyo, Cancer Institute Hospital of Japanese Foundation for Cancer Research and Yamaguchi University. We will conduct the study in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects. The results of this study will be submitted for peer-reviewed publication and presentation at local, national and international scientific meetings and conferences.

Trail registration number UMIN000040032; Pre-results.

Strengths and limitations of this study

- This is the first study to assess the feasibility and efficacy of Cancer and Living Meaningfully (CALM) in Japan, and this preliminary result will inform the conduct of the phase 3 randomised controlled trial of CALM that is planned in Japan.
- This study has no control group and may include a large number of patients with lung cancer as the majority of its participants.
- Quantitative and qualitative approaches will be used to assess the study outcomes, which are rates of completion and improvement of depressive symptoms at 6 months as the primary outcomes, and include death anxiety, quality of life, attachment security and satisfaction with CALM as the secondary outcomes.
- This study is using a Japanese version of the Patient Health Questionnaire-9, which has been already validated.
- This study will be conducted at three medical institutions which enable various diseases to be treated comprehensively, each of which is a prefecture-designated cancer care hospital (regional core hospital) and has more than 686 beds.

INTRODUCTION

Patients with advanced and terminal diseases experience existential distress as a result of a shortened lifespan, prognostic uncertainty, altered interpersonal relationships, and impaired physical functioning, sense of autonomy and personal control.¹ The existential challenges include the threat of impending mortality; loss and changes in appearance or function; loss of freedom of choice, control in life and self-dignity; loneliness; and search for meaning in life.²



Depression has been viewed as a final common pathway of distress in response to these challenges³ and can have adverse effects in such individuals as impaired quality of life,⁴ risk of suicide⁵ and psychological burden on their family.^{6,7} Therefore, an important question in clinical oncology practice is which interventions are most acceptable and feasible for the treatment of depression in patients with advanced cancer.⁸

Previous studies have shown that patients with cancer prefer psychotherapy to pharmacotherapy for the treatment of depression.^{9,10} High attrition rates have been found in group interventions¹¹ and, in a large randomised controlled trial (RCT), cognitive-behavioural therapy was not found to be effective in this population.¹² Benefit has been found from meaning-based individual psycho-educational interventions¹³ and from legacy-based interventions for individuals near the end of life.¹⁴ However, there are few evidence-based psychotherapies that can be delivered in a brief and flexible manner integrated with cancer care from the time of diagnosis and through the trajectory of advanced disease.^{15,16} Further, there are few evidence-based interventions that have been available in Japan to address spiritual pain, other than in hospices for patients near the end of life.¹⁷⁻¹⁹ In particular, psychotherapies dealing with pre-end-of-life spiritual care are rarely performed.

Managing Cancer and Living Meaningfully (CALM) is a novel, brief and manualised psychotherapeutic intervention intended to treat and prevent depression; pre-end-of-life and end-of-life distress in patients with advanced cancer.²⁰ On the basis of relational, attachment and existential theory, CALM deals with distress resulting from physical, psychological, social and spiritual pain. Studies conducted over the past decade have shown that CALM is a feasible, acceptable, and effective therapy for patients with advanced or metastatic cancer.²¹⁻²⁷ In a RCT on the effectiveness of CALM, the CALM group reported less severe depressive symptoms at 3 and 6 months after beginning the treatment compared with those who received the usual care.²³ Although CALM has been practised in more than fifteen countries, including Canada, Germany, Italy and China, it has not yet been implemented in Japan. In addition, studies investigating the effectiveness of CALM have been conducted in just four of these countries.^{23,25-27} It is important to determine the feasibility and potential benefits of CALM in Japan due to cultural differences, particularly related to caution about open discussion of dying and death in Japan.²⁸ This is important to clarify, since a reduction in death anxiety has been a consistent finding in clinical trials of CALM conducted in North America and Europe.^{22,23,25}

The main aim of this study is to examine the feasibility and preliminary efficacy of CALM among Japanese patients with cancer in a phase 2, a single-arm clinical trial. The main hypotheses are that CALM will be also feasible in Japan and improve depressive symptoms in patients with advanced cancer. The study's second aim is to examine whether CALM relieves end-of-life-related

distress, including spiritual pain. The secondary hypotheses are that CALM will be associated with reduction in attachment insecurity and death anxiety and an increase in quality of life and spiritual well-being.

METHODS

Study setting

Participants will be recruited from May 2020 to December 2023 at the Department of Respiratory Medicine in The University of Tokyo Hospital, the outpatient clinic for Psycho-oncology at the Department of Stress Sciences and Psychosomatic Medicine in The University of Tokyo Hospital, the Department of Psycho-Oncology in the Cancer Institute Hospital of Japanese Foundation for Cancer Research, and at the Department of Neuropsychiatry in Yamaguchi University Hospital, Japan, after approval from each ethics committee.

Patient and public involvement

Patients and the public will not be involved in the design, reporting, or dissemination plans of this study. However, general public representatives are members of the Research Ethics Committee of The University of Tokyo, Cancer Institute Hospital of Japanese Foundation for Cancer Research and Yamaguchi University.

Eligibility

Inclusion criteria

All patients should meet the following criteria: (1) ≥ 18 years of age; (2) fluent in Japanese; (3) able to provide written informed consent; (4) have been diagnosed with advanced or metastatic solid-tumour cancer (eg, stage III or IV lung or ovarian cancer, any stage of pancreatic cancer (due to the aggressiveness of this disease), unresectable cholangiocarcinoma, unresectable liver cancer, other stage IV gastrointestinal, gynaecological, breast, genitourinary, sarcoma, melanoma or endocrine cancer) and (5) expected survival is 6 months or more.

Exclusion criteria

The exclusion criteria will be as follows: (1) major communication difficulties with therapists; (2) inability to participate in 3-6 psychotherapy sessions (eg, too ill to engage, lack of means of transportation, insufficient motivation to take part); (3) cognitive impairment and (4) cases in which the therapist indicates pharmacotherapy as a priority treatment for the patient during the first interview.

In Japan, the enrolment rate for compulsory education has been reported to be close to 100% since at least 1948.²⁹ Health insurance is mandatory and covers virtually all residents of Japan, and low-income earners also receive free and equal medical care.³⁰

Interventions

CALM is a semistructured, manualised, individual psychotherapy programme designed for patients with advanced cancer.²⁰ It has some features in common with manualised

supportive-expressive,^{31–35} cognitive-existential^{36–37} and meaning-centred³⁸ group psychotherapies. CALM was developed based on empirical and clinical data, and the theoretical foundations of relational,³⁹ attachment⁴⁰ and existential⁴¹ theories.

CALM comprises 3–6 individual therapy sessions, each lasting approximately 45–60 min, provided over 3–6 months.^{22–23, 42} Additional sessions are provided if it is deemed clinically necessary to meet the needs of the patient. The sessions cover the following four domains: (1) symptom management and communication with healthcare providers; (2) changes in self and relations with close others; (3) sense of meaning and purpose; and (4) the future and mortality.²⁰

Each patient and their CALM therapist explore all of the domains; however, the sequence and time devoted to each domain may vary based on the patients' needs and preferences. The patients' caregivers or families are encouraged to participate in one or more of the therapy sessions, but this is not compulsory.

In this study, CALM will be delivered by therapists—psychiatrists or psychosomatic physicians—who have trained in one or more CALM workshops (in Toronto or other cities) and have been supervised by G. Rodin (in person or online), who is one of the main CALM trainers and developers. Similar to the previous studies, all therapists have over 5 years of clinical experience with psycho-oncology.²²

A qualitative pilot study demonstrated that CALM was associated with profound and unique patient-identified benefits, addressing the multiple practical, relational and existential challenges that both they and their families face. No patient-identified risks or concerns were identified.²¹ Participants in this study reported that they considered CALM a 'safe place,' in which these issues could be 'verbalised' and processed through a dialogue with a trained health professional. Participants were allowed to discuss death and dying as part of the agenda and, thereby, experienced a 'huge relief'. Moreover, they felt regarded as 'a whole person' by their CALM therapists.²¹

Study procedure

First, eligible patients will be identified and approached to discuss their participation in the study. Researchers will ask the eligible patients' doctor to give their patients a brief description of CALM. Despite the ample time required (45–60 min per one CALM session), patients can receive psychotherapy at a cost through their insurance coverage. Whenever possible, CALM sessions will be held on the same day as their examination or consultation with the attending doctor to improve adherence to the intervention protocols. CALM therapists will explain the outline of the study to the eligible patients who are interested in CALM using detailed explanatory documents about this study.

Second, eligible patients will provide written informed consent, agreeing to participate and be audiorecorded. CALM sessions will be audiorecorded to ensure quality

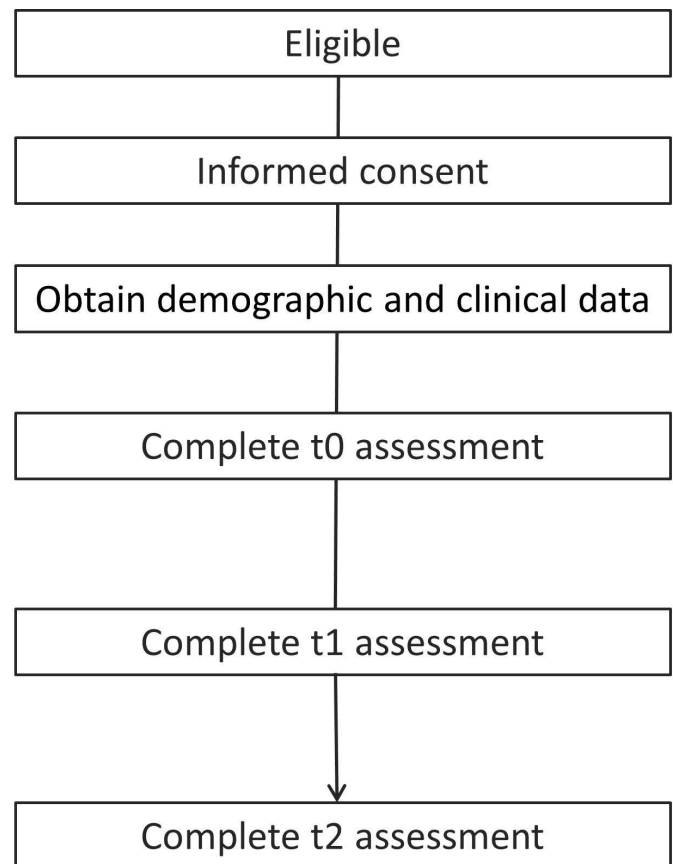


Figure 1 Participants timeline. Participants will have 3–6 individual therapy sessions, delivered over 3–6 months and be asked to complete questionnaires at baseline (t0), 3 months (t1) and 6 months (t2). T0, baseline assessment; T1, 3 months assessment; T2, 6 months assessment (primary outcomes).

control of the intervention. At least 10% of the recorded data can be transcribed, translated into English, password-protected and shared among the team members (CALM therapists and CALM trainers) involved in this study. Discussing the content of the session will help maintain the quality of the CALM session. After case presentations, CALM trainers will use a treatment integrity rating scale to assess the CALM therapists, and these evaluations will be discussed to improve competencies.^{23–43} Eligible patients will be recommended to discuss their decision to participate with their families. Further, if they want to withdraw from the study, participants will be able to send the withdrawal consent form to the researchers or to their doctors.

Third, the participants will be assigned to a therapist to begin CALM therapy. They will be asked to complete questionnaires at baseline (t0), and 3 months (t1) and 6 months (t2) post-CALM (figure 1). Participants will complete the questionnaires in the waiting room, at the examination room after the CALM session at the facility or at home. CALM therapists will ask participants for any missing data (eg, questionnaires) after they complete the questionnaires or at the beginning of the next session. The completed questionnaires will be collected by the CALM therapist and stored in the Department of Stress

Sciences and Psychosomatic Medicine, The University of Tokyo. The possible reasons for potential dropouts during follow-up sessions will be investigated.

OUTCOMES

Primary outcomes

The primary outcomes are the rates of completion of assessment at t2 and improvement of depressive symptoms, measured using the Patient Health Questionnaire-9 (PHQ-9).

The PHQ-9 is a reliable and valid 9-item measure of depression^{44–46} that has been used widely in patients with advanced cancer and for which there is a validated Japanese version.^{47 48} The summed score ranges from 0 to 27, with higher scores indicating higher depressive symptoms.

Outcomes will be assessed at t0, t1 and t2. The primary outcomes will be assessed at t2 for participants who were able to complete at least three CALM sessions,²³ which is the minimum quantity of therapy. The criteria for successful rate of completion is that at least 70% participants who undergo more than three sessions, will be assessed at t2.⁴⁹ If participants express their need for further treatment, CALM will continue.

Secondary outcomes

Secondary outcomes are the rates of improvement in the pre- to post-intervention scores on the following psychosocial measures: (1) the Quality of Life at the End of Life-Cancer Scale (QUAL-EC), (2) the Experiences in Close Relationships scale (ECR-M16), (3) the Death and Dying Distress Scale (DADDS) and (4) the Clinical Evaluation Questionnaire (CEQ).

The QUAL-EC is a measure of quality of life in patient populations with life-threatening illnesses near the end of life. It has four subscales⁴: (I) Symptom control (eg, list of physical symptoms each patient experienced in the last week and their frequency, severity and interference), (II) Relationship with healthcare providers (eg, 'I have a sense of control about my treatment decisions,' 'My doctor has a sense of who I am as a person beyond my illness'), (III) Preparation for the end-of-life (eg, 'I worry that my family is not prepared to cope with the future,' 'At times, I worry that I will be a burden to my family'), and (IV) Sense of life completion (eg, 'I have been able to say important things to those close to me,' 'I have been able to share important things with my family').

The ECR-M16 is a validated 16-item scale, which measures attachment insecurities of patients with advanced cancer or their ability to rely on close people for support.⁵⁰ The subscale scores assess attachment anxiety (eg, 'I worry about being abandoned') and avoidance (eg, 'I try to avoid getting too close to other people').

The DADDS is a validated 15-item scale, which measures death anxiety in patients with advanced cancer.⁵¹ The DADDS assesses fears about the dying process and distress about lost opportunities and self-perceived burden to

others as a result of impending mortality (eg, 'Not having done all the things that I wanted to do,' 'The impact of my death on my loved ones').

The CEQ is a seven-item measure which was developed by the CALM development team in Canada.⁴² The CEQ will be used to evaluate the extent to which patients feel supported by their CALM therapist. It includes questions that assess patients' ability to cope with future prospects, discuss important things with close people and increase in double awareness (eg, deal with changes in my relationships as a result of cancer, express and manage my fears about dying). The CEQ has a free entry field, allowing participants to share any comments (positive or negative) about their CALM therapy.

The QUAL-EC, ECR-M16, DADDS and CEQ have been translated into Japanese and a final version was developed after further discussion and consensus among the authors, who were native Japanese speakers and had expertise in psycho-oncology. This version was back-translated into English by a professional bilingual editor, proficient in both English and Japanese, to confirm that the English and Japanese versions were conceptually equivalent. These Japanese version scales required only minor changes. Validation studies of the Japanese version of QUAL-EC, ECR-M16, and DADDS are currently being conducting in Japan.

Power calculation of sample size

To perform the power calculation, we used the differences in PHQ-9 scores (primary outcome) between the baseline and 6 months in a previous study²² in which the calculated sample size included 34 participants (significance level: 0.05, power: 0.8, standardised estimate: -0.13). The rate of participation in at least three sessions in the previous study was 0.744. Therefore, we divided the sample size by the rate of completion ($34/0.744=45.7$) to derive 46 participants as this study's target sample size.

Statistical methods

Each outcome will be expressed in terms of mean±SD. The PHQ-9 scores between baseline (t0) and 6 months (t2) will be analysed using paired sample t tests.

We will use multilevel modelling^{52–54} as subanalyses to predict the trajectory of each variable (scores from the questionnaires) due to repeated measurement data and the hierarchy. Multilevel modelling uses all available data, and patients who provide only partial data over the study period will be retained in the analysis. The multilevel modelling will show whether there are significant changes in outcomes over time. All p values will be two-tailed tests and considered to be statistically significant at <0.05. We will also analyse those individuals who complete at least three sessions of CALM therapy using SAS (V.9.4).

Ethics and dissemination

Research ethics approval and protocol amendments

This study was approved by the Research Ethics Committee of the University of Tokyo (2019345NI) (Protocol Version

3.0; 23 March 2020), the Cancer Institute Hospital of Japanese Foundation for Cancer Research (2020-1241), and Yamaguchi University (2021-081). Modifications to the protocol will be shared promptly at these facilities and communicated to relevant parties immediately, including the participants, journal and ethics committees.

This study was conducted in accordance with the Declaration of Helsinki⁵⁵ and the Ethical Guidelines for Medical and Health Research Involving Human Subjects.^{56 57}

Consent or assent

The explanatory documents and consent forms (online supplemental materials 1 and 2) provided to the participants will describe the study, its objectives and the potential benefits/risks. They will also indicate that withdrawal from the study will not affect their current or future clinical care and explain what steps will be taken to maintain their confidentiality of the data. However, we will explain to the participants that the results already presented at academic conferences and papers before withdrawal of consent, will not be retracted. Participants will also be informed that if the study causes health damage, they will receive general medical care as compensation. Patients will be recommended to inform their family about participation. After the eligible patients have signed the consent forms, one copy will be given to the patient and the original will be collected and kept by the CALM therapists. The consent forms will be retained at each research facility.

Data management and confidentiality

Clinical data (gender, age, diagnoses, date of diagnosis, information on limited life expectancy, spouse and family structure, education, recorded audio files and questionnaire data) that are obtained from this study will be managed anonymously by a data manager. All participants will be assigned a unique subject identification number (ID), and all records will be affiliated with this number. All data will be coded by the ID, and all study-related documents will be anonymous. The consent forms containing participants' signature and the master lists linking participants' names to the ID numbers will be stored in secure servers or in locked office filing cabinets. Finally, the stored data will be analysed by the researchers. The principal investigator and researchers who will analyse the data will have access to the final dataset. The results will be submitted for peer-reviewed publication and presentation at local, national and international scientific meetings and conferences.

Expected advantages and disadvantages

Patient benefit

There is a significant association between depression and advanced or metastatic cancer⁵⁸; however, depression tends to be undetected and untreated in this population.^{59 60} There is little evidence for the benefit of antidepressants compared with placebo in patients with advanced cancer.⁶¹ A disadvantage of both antidepressants and anxiolytics in advanced cancer is the substantial side effects which include seizures, thirst, sexual

dysfunction, headaches, suicidal tendency, organ damage or interactions with anticancer treatments.^{62 63} Many Japanese patients also hesitate in taking psychiatric drugs because of prejudice or stigma.⁶⁴⁻⁶⁶ It is also possible that they doubt that professional help can relieve their distress.³ Despite these barriers, it has been reported that Japanese patients with cancer prefer psychotherapy to drug therapy as a treatment for depression, as in previous international studies.⁹

The expected advantages of providing CALM in Japan are as follows: (1) CALM helps patients avoid the side-effects of psychotropic drug therapy; (2) patients with cancer recognise it as a holistic; and (3) despite the ample time required (45–60 min per one CALM session), patients can receive psychotherapy at a cost through their insurance coverage. Patients' emotional aspects can be cared for more quickly if the session is held immediately after their examination or consultation with the attending doctor, because CALM provides support and resolution of distressing thoughts and emotion caused by various changes associated with cancer.

Previous study reported that the majority of patients with metastatic cancer and clinically significant depressive symptoms were not referred to psychosocial care and most of those referred did not receive specific or adequate treatment for depression.⁶⁷ CALM is designed to address the difficulties and risk factors that contribute to the emergence of depressive symptoms in this circumstance (eg, adverse effects on psychological well-being, quality of life, non-compliance with medical treatment and distress in caregivers).³ CALM provides support and a reflective space for the processing of thoughts and emotions evoked by this traumatic condition. In CALM sessions, patients and therapists have sufficient time to discuss their life and the disease with their therapist. CALM may also be more helpful for patients with advanced cancer who have a longer life expectancy than those who are close to the end of life.¹⁴ Further, it may help patients and their families to prepare for future treatment, improve their quality of life during the remaining days, and facilitate the selection of a more satisfactory and comfortable medical treatment. One of the advantages of this study is using a Japanese version of the PHQ-9, which has been already validated, which will allow us to accurately determine the depressive symptoms of Japanese patients.

Patient disadvantages and how to minimise them

CALM therapists usually explore the topics of life and death and disease-related distress, which could increase some participants' anxiety and mental distress. However, participants have no obligation to discuss such issues, and previous research has shown that death-related distress is decreased by CALM. All CALM therapists have received clinical supervision by the intervention's developers and specialise in palliative care, psychosomatic medicine or psychiatry. Considering the possibility that participants may experience emotional stress as a result of the therapy, the therapists will pay particular attention to participants'



mental and physical state in this study. Moreover, the participants will receive standard care (eg, drug administration) at the Department of Stress Sciences and Psychosomatic Medicine in The University of Tokyo Hospital; the Department of Psycho-Oncology in the Cancer Institute Hospital of Japanese Foundation for Cancer Research; and at the Department of Neuropsychiatry in Yamaguchi University Hospital; in case their mental distress exacerbates during or after this study.

The CALM programme allows ample time to discuss the four domains of the intervention. However, even 3–6 sessions over 6 months could be burdensome for some participants. Therefore, patients who cannot commit to the required number of psychotherapy sessions will be excluded at the time of recruitment. In addition, the number of sessions may vary, depending on the clinical circumstances.

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Acknowledgements We would like to thank our research staff for their valuable contributions to this study. We would also like to thank Goh Tanaka, Yosuke Amano, Hiroyuki Tamiya, Yoshihisa Hiraishi, Keita Maemura, Naoya Miyashita, Takahiro Ando, Keisuke Hosoki, and Hiroaki Abe for lending their expertise on the application of CALM. Finally, we would like to thank Editage (www.editage.com) for English language editing.

Contributors All authors contributed to refine the study protocol and approved the final manuscript. And the roles and responsibilities are as follows: SM conceived and designed the study, and will recruit the participants, provide CALM therapy to the participants, collect, manage and analyse the data, and write the paper. TY conceived and designed the study and will provide CALM therapy to the participant. KS is a grant holder and conceived and designed the study, will recruit participants, provide CALM therapy, collect data, and manage the data. TM is a grant holder and will recruit participants, provide CALM therapy, collect data, and manage the data. HKa and KW will provide respiratory expertise and recruit participants. HKo will recruit participants. YM will provide statistical expertise in analyzing the data. GR developed CALM therapy. He will also supervise and provide CALM therapy. KY is the principal investigator and helped conceive and designed the study, and will analyse the data, and write the paper.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s)

Provenance and peer review Not commissioned; externally peer reviewed.

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