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The menopause after cancer study (MACS) - A multimodal technology assisted intervention for the management of menopausal symptoms after cancer – Trial protocol of a phase II study

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ABSTRACT

Aims: This study will aim to assess if a composite intervention which involves a specific evidence-based intervention for management of insomnia and non-hormonal pharmacotherapy to manage vasomotor symptoms (VMS) of menopause can improve quality of life for patients experiencing troublesome VMS after cancer who are not eligible for standard systemic menopausal hormone therapy (MHT). Participants will be asked to nominate a partner or companion to support them during this process as an additional form of support.

Background: The menopause transition and its symptoms represent a significant challenge for many patients after cancer treatment, particularly those for whom conventional MHT is contraindicated. These symptoms include hot flushes, night sweats, urogenital symptoms as well as mood and sleep disturbance. These symptoms can exacerbate the consequences of cancer and its treatment.

Methods: We will recruit 205 women who meet inclusion criteria and enrol them on a composite intervention which consists of four parts: (1) use of non-hormonal pharmacotherapy for the management of troublesome vasomotor symptoms of menopause tailored to the timing of predominant symptoms, (2) digital cognitive behavioural therapy for insomnia through the web based Sleepio service, (3) access to information regarding self-management strategies for the common symptoms of menopause and their consequences and (4) identification of a partner or other support person who commits to providing support during the study period.

Outcomes: The primary outcome will be cancer specific quality of life measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ C30). Secondary outcomes will include sleep quality, bother/interference of vasomotor symptoms and communication between couples about their cancer diagnosis and their menopause experience. Sleep will be measured using the Sleep Condition Indicator (SCI) tool, bother/interference of vasomotor symptoms will be measured by the Hot Flush Rating Scale (HFRS) and communication will be measured using the Couples' Illness Communication Scale (CICS). These validated scales will be administered at baseline, four weeks, three months and six months.

Registration: This study is registered on ClinicalTrials.gov with number NCT 04766229.

1. Introduction

As the rates of many types of cancer increase globally, so too do the numbers of people surviving. This may, in part, be due to improvements in treatments and earlier detection of disease as well as increasing life span. However, treatments can have persistent physical, psychological and emotional effects which may severely affect quality of life beyond the original cancer diagnosis. In Ireland, there are 173,000 survivors of cancer, approximately 4% of the population, and this number is set to double over the next 25 years [1]. Therefore, it is of increasing importance to prioritise 'survivorship' or living with, through and beyond cancer in our overall national approach to cancer care.

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Menopause after cancer treatment is a significant issue facing many women as part of life beyond cancer. Menopause, the final menstrual period, is accompanied by an array of symptoms including vasomotor symptoms such as hot flushes and night sweats as well as urogenital symptoms such as vaginal dryness which may cause sexual dysfunction [2]. The menopause and its symptoms may be induced by many cancer treatments such as pelvic radiotherapy, chemotherapy or surgical removal of the ovaries in premenopausal women. Symptoms can also be exacerbated by maintenance treatments for certain hormone sensitive cancers or indeed by the withdrawal of previously instituted menopausal hormone therapy (MHT) which is contraindicated following diagnosis of some cancers [3]. Evidence suggests menopause after cancer can be more severe and persistent than at natural menopause [4,5]. Vasomotor symptoms may impact on sleep, mood and overall quality of life, adding to the burden of cancer and its treatment [6].

The relationship between the menopause and sleep is a complex interplay between vasomotor symptoms, neural changes and insomnia symptoms [7]. Other common symptoms such as low mood and pain can further complicate this relationship.

We know these symptoms are problematic for women in Ireland. A recent survey of 400 women after cancer showed that hot flushes, poor sleep, and fatigue were the three main symptoms that troubled patients. Twenty-percent of those surveyed were on MHT. More than two thirds of those surveyed had a history of breast or other hormone sensitive cancers and as such MHT is likely contraindicated for these women. Hot flushes were associated with impaired concentration, sexuality and reduced overall enjoyment of life in up to one third of women surveyed [8].

The presence of illness within a partnership can often change the equilibrium of that relationship. Open communication between couples about illness is equally important for both parties. Close relationships can be a source of emotional and practical support for both patient and partner during the cancer experience and help them cope with the stressors that come with a cancer diagnosis, treatment and recovery [9]. An inability to talk openly can increase psychological distress and distancing within a relationship. Indeed, avoidance of discussing illness-related issues has been associated with increased distress and lower relationship satisfaction for both partners [10]. Although it is difficult to address the impact of the presence of a partner on oncological outcomes, a number of studies have demonstrated that married patients with cancer have a better prognosis than single, widowed or divorced patients with cancer [11–14].

This study will address the three leading priorities for Irish women cancer survivors. We will focus on vasomotor symptoms in women who are ineligible for estrogen-containing menopausal hormone therapy. We will enrol them in a specific intervention designed to improve quality of life by managing vasomotor symptoms and improving sleep hygiene. Furthermore, we will assess if the presence of a peer-identified support person impacts on quality of life. Our primary aim is to determine whether this composite intervention improves quality of life for women with troublesome vasomotor symptoms after cancer over a six-month period.

2. Material and methods

2.1. Study design

This study will be a single arm phase II trial employing a pre-test post-test design. This design has been chosen to ascertain the appropriate effect sizes to inform a randomised controlled trial in the future.

The composite intervention consists of four parts: (1) use of non-hormonal pharmacotherapy for the management of troublesome vasomotor symptoms of menopause tailored to the timing of predominant symptoms, (2) digital cognitive behavioural therapy (CBT) for insomnia through a web based service called Sleepio, (3) access to information regarding self-management strategies for the common symptoms of menopause and their consequences through an app called myPatientSpace and (4) identification of a partner or other support person who commits to providing support during the study period.

Women who satisfy the inclusion and exclusion criteria will have quality of life, sleep dysfunction, bother or interference of vasomotor symptoms and the communication between them and a partner or other support person about their diagnosis and menopause, assessed at baseline and again at four weeks, three months and six months using validated scales (see Fig. 1). Cancer quality of life will be measured using the European Organisation of Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ C30) instrument [15]. Sleep will be assessed using the Sleep Condition Indicator (SCI) [16] survey while bother/interference of vasomotor symptoms will be measured using the Hot Flush Rating Scale [17]. Communication will be measured using the Couples' Illness Communication Scale (CICS) [18]. The CICS scale has been adapted to include questions about the extent to which couples discuss the participants menopause as well as her cancer.

Our study aims to ascertain if quality of life can be improved for women dealing with menopausal symptoms in the context of a prior cancer diagnosis by ameliorating the impact of VMS and improving sleep.

We will offer non-hormonal pharmacotherapy (either citalopram/venlafaxine or gabapentin) for troublesome vasomotor symptoms. These agents have been shown to be effective for vasomotor symptoms and may also improve mood, sleep and quality of life [2] [19–24].

These treatments are recommended by the North American Menopause Association [21], the Australasian Menopause Association [25] and the American College of Obstetricians and Gynaecologists [26] for the non-hormonal management of menopausal symptoms. Furthermore, the American Cancer Society and the American Society of Clinical Oncology have recommended use of both of these medications to help mitigate the vasomotor symptoms of menopause in breast cancer survivors [27].

These treatments can be used as monotherapy or in combination. We will personalise medication to the most bothersome vasomotor symptom (see Fig. 2). If symptoms are mostly in the day, patients will be prescribed the selective serotonin reuptake inhibitor (SSRI) citalopram, starting at a dose of 10 mg which can be increased to a maximum of 30 mg, if required [19,20,28,29]. Dose increase to 20 mg will be considered after 2 weeks based on clinical response [19]. Many women who have a diagnosis of breast cancer may be prescribed adjuvant endocrine therapy in the form of tamoxifen. There is a theoretical interaction between tamoxifen and some medications in the SSRI class of drugs [30]. However, it is unclear if this is clinically relevant [31]. Equally, the use of the specific SSRI citalopram, intended for use in this study, has been shown not to affect outcome in patients taking tamoxifen [32,33]. Furthermore, the international menopause and oncology societies mentioned above do not warn against the use of citalopram in patients taking tamoxifen.

Nevertheless, in view of some physicians reticence in the use of these drugs in patients on tamoxifen we will permit the use of the Serotonin Noradrenaline Reuptake Inhibitor (SNRI) venlafaxine depending on physician preference in this study.

If symptoms are most bothersome at night, patients will be prescribed the anticonvulsant gabapentin starting at a dose of 300 mg 1 h before bedtime increasing by 100 mg every three nights until relief of hot flushes, onset of side effects, or a maximum of 900 mg is reached [34]. If symptoms are equally bothersome during the day and at night-time, the medications can be used in combination. In this situation, patients will commence on 10 mg Citalopram in the morning and Gabapentin 300 mg at bedtime for 3 days, then twice daily for 3 days, and then 3 times a day thereafter [35].

CBT interventions for sleep dysfunction have been shown to be effective in people with cancer [36] and for menopause related sleep difficulties [7], making CBT the first line treatment for insomnia. Participants will be given access to an online cognitive behavioural therapy (CBT) program for insomnia (Sleepio). Sleepio is delivered through a

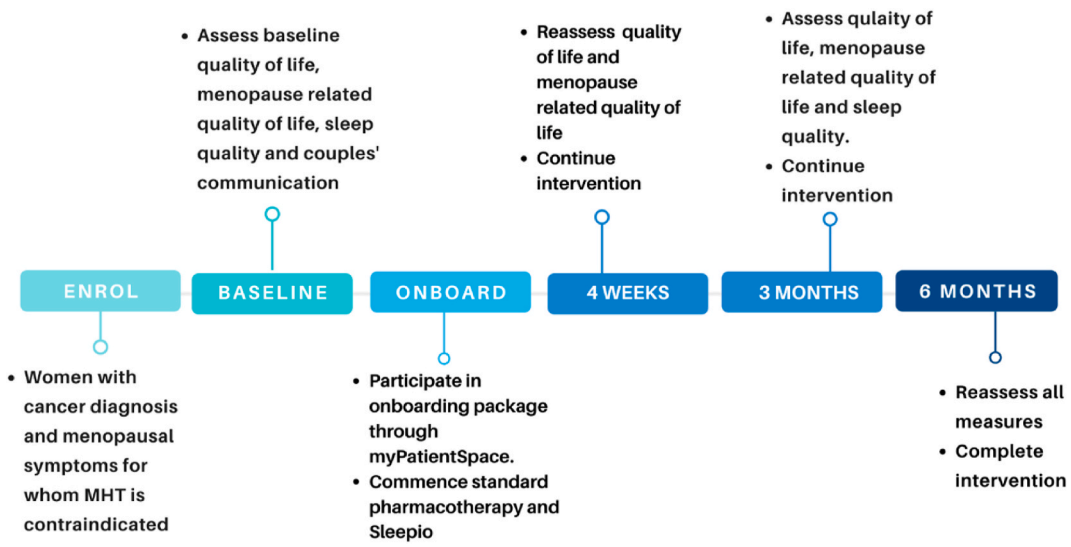

Fig. 1. Study overview.

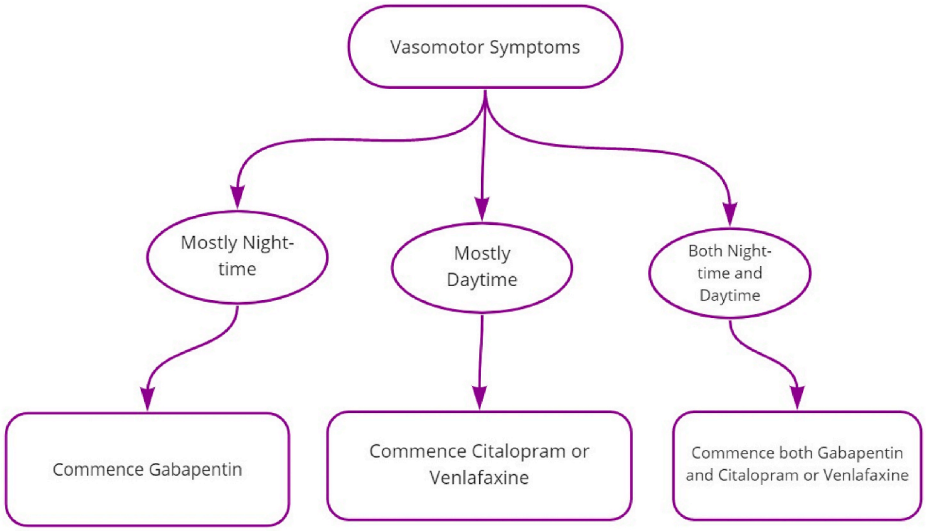

Fig. 2. Medication algorithm.

fully automated media-rich web-based application or mobile enabled webpage over a minimum of six weeks. It is driven dynamically by baseline, adherence, performance and progress data obtained through the completion of sleep diaries. These facilitate personalised tailoring of the CBT programme to the user's specific needs. The programme is moderated by a virtual therapist and uses multiple CBT based strategies to improve sleep quality. In randomised controlled trials, Sleepio has demonstrated efficacy for insomnia disorder and sleep disturbance associated with depression. Sleepio improves sleep efficiency, sleep onset latency and wakefulness after sleep onset [37–40]. This will be the first time that Sleepio has been trialled in a cancer population.

Within the myPatientSpace app, we will provide written information regarding the common symptoms of menopause that are encountered by patients who have had treatment for cancer and offer simple self-management strategies to manage many of them. For example, we will provide written information about issues such as bladder problems, memory and stress and emotional worries with links to podcasts and videos tailored specifically to people who have menopausal symptoms in the context of a prior cancer diagnosis.

The partner aspect of the study is an exploratory optional element to the study. Each participant will be asked if they wish to identify a partner or support person who will support them during the study. We will assess to what extent each patient discussed her experience of menopause and cancer with this person through the use of a validated scale. We will ask each partner or support person the same questions and examine if there is concordance between both parties and examine if this changes over the course of the study.

The expected study duration is from June 2021 to July 2022. Ethical approval has been obtained from the Research Ethics Committee of St. Vincent's University Hospital, Dublin, Ireland (reference number RS21-002) and is under review with the Institutional Review Board of the Mater Misericordiae University Hospital, Dublin, Ireland.

2.2. *Participants*

Participants will include women aged 18 and over who are experiencing troublesome vasomotor symptoms of menopause in the context of a current or prior history of cancer. Troublesome symptoms will be defined as at least five moderate or severe hot flushes during the day including at night with at least moderate degree of bothersomeness (sum score greater than or equal to 5.3 on the bother subscale of the Hot Flush Rating Scale) [41]. Participants must have a contraindication to MHT on

any grounds and be competent in spoken and written English and in the use of the internet and smartphone devices. Given the inclusion criteria and the symptoms under investigation we envisage that the vast majority of recruited patients will have a history of breast cancer. This is because breast cancer is the most common female cancer, it's treatment often involves the use of agents which may induce menopausal symptoms and MHT is generally contraindicated after breast cancer. We anticipate that there will be a smaller group of patients with gynaecological cancer as MHT can often be used safely after a diagnosis of gynaecological malignancy [42].

The exclusion criteria for the study include having a Eastern Co-operative Oncology Group (ECOG) performance status [43] of 3 or more, meaning the participant must be at least capable of all self-care. Participants who have used either study medication for the indication of managing vasomotor symptoms of menopause or CBT for insomnia in the preceding six months will be excluded. Anyone with a contraindication to the study medications will also be excluded, along with those who are not proficient in English or use of the internet or who do not have access to a smart phone or similar device. Participants with current major mental illness which would limit their participation will also be excluded.

2.3. Power analysis and sample size

Determining appropriate sample sizes for quality-of-life studies depends on baseline reference values for quality of life in the patient population in question as well as what are considered clinically relevant changes. Early work from the EORTC quality of life group indicates that mean changes of 5–10, 10–20 or more than 20 points in individual scores could be considered small, medium and large in a breast cancer population [51]. Considering clinically relevant changes rather than statistically significant changes has been reported to be poor in quality of life studies in general [52] and there is wide heterogeneity between how results are statistically analysed also [53]. More recent evidence based guidance suggests specific ranges for differences in means between groups for each specific functional or symptom scale within the EORTC-QLQ-C30 [54]. For the global quality of life scale, changes of 4–10, 10–15 and more than 15 are considered small, medium and large, respectively. Later work from the same authors [55] suggests ranges of observed change specific to each scale and specific to whether the observed change was an improvement or a deterioration. For example, for the global quality of life scale, an improvement of 0–5 points would be a trivial change, while an increase of between 5 and 8 points would be considered small. A change of more than 8 points would be a medium sized improvement. Large size improvements could not be estimated. The authors suggest that if a study is being powered to detect the smallest clinically relevant change then the threshold between trivial and small ranges should be selected to perform the power calculation. For the quality-of-life scale, which is relevant to this study, this would be 5.

Baseline scores in the scale are also relevant to sample size calculations. The 2008 EORTC reference values manual compiles available data to give an idea of mean values for each of the symptom and functional scales within the EORTC-QLQ-C30 [56]. For this study the functional scale of global quality of life is of principal concern. Given the inclusion criteria, we expect the majority of our patients to be women with a past or current history of breast cancer, both early and metastatic. With this in mind, we note that the 2008 reference value for mean global quality of life in all women with breast cancer was reported as 61.8 with a standard deviation of 24.6 [56]. It is worth noting that 41% of those included within this data had recurrent or metastatic disease. If considering just stage I or II disease (17% of those included in this reference manual data) the mean global quality of life score is 64.6 with a standard deviation of 22.7.

These reference values have been considered in breast cancer more recently also [57]. Here breast cancer patients were subdivided into early breast cancer (EBC) or metastatic breast cancer (MBC). Data was collated from an EORTC registry of trials and also in another registry of cancer trials called Project Data Sphere (PDS). Baseline global quality of life in the EBC EORTC cohort was 76.9 with a standard deviation of 19.2. In the PDS cohort the baseline score for the global quality of life scale was 72.4 with a standard deviation of 18.8. Together, these 2 databases consist of RCT data from more than 5000 women with EBC.

In MBC, as expected, the baseline level was lower at 57.6 with a standard deviation of 23.1. in the EORTC registry of trials. In the PDS database, the baseline level was 54.6 with a standard deviation of 20.1. This cohort consists of 434 women.

As we will be recruiting women with both EBC and MBC as well as those with other cancers we estimated the mean pre-treatment EORTC-QLQ-C30 quality of life score in this cohort of women will be 65 (SD 20). This is an average of the value for EBC and MBC. To detect a 5-point improvement with 90% power and a two-sided 5% significance level requires a minimum of 171 patients. To account for a 20% drop out rate, we plan to recruit 205 participants.

2.4. Recruitment

The expected accrual rate is six to ten patients per week from June 2021 until January 2022. This is based on significant clinical need for management strategies for these patients. The limit on recruitment is based on available time resources to recruit patients to the study. Our main recruitment strategy is through education of treating physicians, nurses and allied health professionals in areas such as medical oncology, breast surgery, radiation oncology and gynaecology of the inclusion and exclusion criteria. Advertisements in clinic waiting rooms and other areas eligible patients are likely to frequent will also be used and patients can self-refer for consideration of inclusion. We will utilise social media to advertise the study to physicians, patients, and patient advocates for wider dissemination.

2.5. Procedure

All potential participants will be screened by a member of the research team via telephone to ensure all inclusion criteria and exclusion criteria are met. Willing participants who fulfil the criteria will be consented by a member of the research team. Once informed written consent has been signed by both the participant and the researcher, baseline demographic and prior health history data will be collected according to a predefined minimum dataset. Participants will be given access to an app called myPatientSpace which contains a facility created specifically for this study. Participants will complete their baseline outcome measures through this app and will then commence the therapeutic interventions. All recruited patients will also be given a code to gain complimentary access to Sleepio.

2.6. Intervention

Participants will remain on the intervention for six months and have quality of life, interference/bother of vasomotor symptoms, sleep and communication assessed using validated scales at baseline, four weeks, three months, and six months.

2.7. Measures

2.7.1. Primary outcome

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) instrument is a multidimensional, validated, cancer-specific quality-of-life questionnaire developed by the EORTC Study Group on Quality of Life for use in international clinical trial settings [15]. The questionnaire is designed for use with a wide range of cancer patient populations, irrespective of specific diagnosis. It can be supplemented by optional questionnaire

modules, which are developed for specific diagnostic groups or for specific treatment modalities. The EORTC QLQ-C30 includes 5 functional scales (physical, role, emotional, social and cognitive functioning), 3 symptom scales (fatigue, pain, and nausea and vomiting), a global health status/quality of life scale, and a number of single items assessing additional symptoms (dyspnoea, sleep disturbance, constipation and diarrhoea) and perceived financial impact. For the majority of the EORTC QLQ-C30 items a 4-point Likert-type response scale is used. The only exception is the global health status/quality of life scale (where a 7-point scale is used). For ease of presentation and interpretation, all subscale and individual item responses are linearly converted to a 0 to 100 scale. For the functional and global quality of life scales, a higher score represents a better level of functioning. For the symptom scales and items, a higher score reflects a greater degree of symptoms. Changes in the global health status/quality of life scale are the primary focus of investigation in this study and will be assessed at baseline and at the four week, three month, and six month intervals.

2.7.2. Secondary outcomes

There are two secondary outcomes for this study – degree of bother/interference of vasomotor symptoms of menopause and sleep dysfunction. These will be measured using the Hot Flush Rating Scale (HFRS) and the Sleep Condition Indicator (SCI) respectively.

2.7.2.1. Bother/interference of vasomotor symptoms of menopause. The HFRS [17] is a validated self-report measure of frequency and problem-rating of vasomotor symptoms over the preceding week. The problem rating is based on three questions exploring the extent to which participants consider vasomotor symptoms a problem, their degree of distress related to these symptoms and their impact on daily routine. Each of these items is scored on a Likert scale from 1 to 10 with a score of 1 indicating no effect of the symptoms and a score of 10 indicating a significant effect. These three scores are then added together to give an overall assessment of symptom impact with higher scores indicating a more problematic experience of vasomotor symptoms [44].

This scale has been extensively used in studies of vasomotor symptoms both in populations of women in general [45,46] and women with cancer specifically [47,48].

This scale will be administered at baseline and at the four week, three month, and six month timepoints through the myPatientSpace app.

To be considered eligible for inclusion women must experience at least five moderate or severe hot flushes per day including at night with a at least moderate ratings of bothersomeness which is defined as a sum score of greater than or equal to 16 on the bother subscale of the HFRS.

2.7.2.2. Sleep dysfunction. The Sleep Condition Indicator (SCI) is a screening tool for insomnia based on the DSM5 criteria for insomnia disorder. It consists of eight items - two quantitative items on sleep continuity, two qualitative items on sleep satisfaction/dissatisfaction, two quantitative items on severity and two qualitative items on attributed daytime consequences of poor sleep. It has been shown to have good content validity and good concurrent validity with established sleep dysfunction indicators [16,49]. Each item is scored on a five-point scale (0–4), with lower scores in the 0–2 range, reflecting putative DSM-5 threshold criteria for insomnia disorder. Possible total score ranges from 0 to 32, with higher values indicative of better sleep [50]. It has also been previously used in randomised controlled trials which have used the Sleepio platform [38,40].

This scale will be administered at baseline and at the three month and six-month time points, again through the myPatientSpace app.

2.7.3. Exploratory outcomes

The addition of a partner or other support person is a novel aspect of our research study. The communication between this dyad about the participants cancer diagnosis and menopause experience will be assessed using the Couples' Illness Communication Scale (CICS). The CICS is a brief scale developed and tested on a group of women with a diagnosis of ovarian cancer. It has good levels of reliability and validity [18]. It consists of 8 questions, 4 for the patient and 4 for her partner or support person which are scored on a 5-point Likert scale ranging from disagree strongly to agree strongly. Items 1 and 3 are reverse scored. Higher scores indicate a better degree of illness related couples' communication. It is our intention to administer this scale at baseline and at six months. We will adjust the scale slightly to focus on the degree of communication between them specifically around the menopause as well as about their cancer diagnosis in general. This scale will be administered at baseline and at the six-month time point. We will also assess this aspect of our study through qualitative semi-structured interviews with a small number of participants and their partners or support people.

2.8. Discussion

Menopause after cancer is a significant area of unmet need for cancer survivors in Ireland [8]. This study aims to tackle some of the wide constellation of symptoms that menopause presents and that have been identified as priorities in previous surveys of patients [8]. The main target symptoms are vasomotor symptoms of menopause and insomnia which are common in cancer patients.

Each component of our study is supported by robust evidence – SSRIs/SNRIs (e.g. citalopram/venlafaxine) and gabapentin are established as the standard of care for women who cannot have MHT [25–27], CBT for insomnia is the first line treatment for management of insomnia [7] and patients who have good psychosocial support are known to experience better outcomes while undergoing oncology treatment [9–11]. This study ambitiously aims to incorporate these three elements in a composite intervention which is complemented by a companion app which provides a suite of information related to cancer after menopause in general and the study specifically.

Despite this novel approach and robust supporting evidence, this study is not without its limitations. First, the use of a general cancer quality of life measure rather than a menopause specific measure as the primary outcome may limit the ability to identify small treatment effects on menopausal symptoms. However, in order to potentially prove benefit for this intervention and permit further roll out of similar initiatives in this jurisdiction in the future, a more generic outcome measure is preferred to allow interpretation of the findings by a wider audience in more readily understandable terms. Secondly, the non-randomised design was selected as little is known regarding effect sizes in interventions such as this and, thus, powering the study for a randomised design would be impossible. It is intended that a randomised study would be carried out in future based on the results of this phase II intervention.

Specific sleep problems are not an inclusion criterion for the study. This may limit the assessment of the effectiveness of the CBT for insomnia aspect of the study. However, digital CBT for insomnia is a relatively unstudied area and even initial exploratory data on its use could help to design future studies specifically aimed at sleep dysfunction as a challenge of living well with and beyond cancer.

The individual effect of the information included on myPatientSpace will be difficult to measure and control for which may affect the interpretation of results. In addition to this, given the composite nature of the intervention it will be difficult to measure the impact of each part of the intervention has on the final outcome. However, given that this is a phase II study, we can report on engagement with each component of the study and seek participant feedback on which elements of the study they personally found most beneficial to their experience. If overall quality of life is seen to improve, any changes within the different scales within the EORTC-QLQ-C30 questionnaire may help to ascertain what elements were most effective. Both the Sleepio and myPatientSpace elements of the study collect user engagement data and this will be useful

to report on also.

3. Conclusion

Menopausal symptoms after cancer are a major area of unmet need in Ireland. The current research aims to improve quality of life for women experiencing these symptoms who are unable to use menopausal hormone therapy. This intervention includes digital cognitive behavioural therapy for insomnia and psychosocial support from a partner or other support person in addition to the use of standard non-hormonal medications for the management of vasomotor symptoms of menopause.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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