Oral Micronized Progesterone for Perimenopausal Vasomotor Symptoms

NCT01464697

Study Protocol: June 12, 2014
Clinical Research Ethics Board explanation of Amendments: November 18, 2018
Amendments to Study Protocol: November 9, 2018

CeMCOR Protocol: Peri-P-236267-01
Oral Micronized Progesterone for Perimenopausal Vasomotor Symptoms Study

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Funding:

CIHR Operating Grant "Oral Micronized Progesterone for Perimenopausal Vasomotor Symptoms", March 2010 competition, funded for 4 years (CIHR # 221598).
Drug and placebo to be provided by **Besins Healthcare**—see attached letter of collaboration.
The University of British Columbia and CeMCOR will provide research space and facilities to conduct the trial; the investigators have a well-developed network of contacts for efficient recruitment.
Pharmacists at a research pharmacy will dispense drugs according to web-based random therapy allocations.

Summary

This is a randomized, double-masked, placebo-controlled trial of oral micronized progesterone (300 mg at bedtime daily) for hot flushes and night sweats (collectively vasomotor symptoms, VMS) in women stratified to be in Early or Late Perimenopause. We have recently completed a similar trial showing that oral micronized progesterone provides effective therapy for healthy

postmenopausal women with VMS. Currently there is no effective, evidence based treatment for perimenopausal VMS.

Background

1.1 Problem to be addressed

Perimenopausal women urgently need effective therapy to treat VMS. The post-war generation is passing through perimenopause, and evidence-based therapies are lacking. Existing therapies have been developed for and tested on postmenopausal women; none have been performed, thus none are proven effective in *peri*menopause, a life phase during which estradiol levels average at least normal or higher and are highly variable, yet progesterone levels are lower than in premenopausal women. VMS occur in 80% of perimenopausal women—9% of these experience moderate to severe VMS [1]. Oral micronized progesterone (OMP, Prometrium®) is an effective therapy for VMS in healthy women 1-11 years since the final menstrual period. Furthermore, it is effective for frequent and moderate-severe VMS . This is a trial of similar design using oral micronized progesterone for women experiencing perimenopausal VMS.

There is increasing recognition that **VMS are a feature of midlife rather than of old age** and are predominantly experienced by women in the years leading up to and the year immediately following the final menstrual period (perimenopause). A recent meta-analysis of prospective, longitudinal studies estimated VMS to last a median of four years in symptomatic women [2]. Although prospective population-based studies suggest a VMS duration of 5.5 year[3] recently a single cohort study starting earlier in perimenopause indicates those with the earliest onset may have VMS continuing for over 12 years[4]. Most women do recover. VMS symptoms, however, can begin at a much younger age than many people realize; in a Swedish population-based survey, 38% of those aged 46 at the time of the survey reported VMS [5]; 25% of "premenopausal" women (so defined because they were still regularly menstruating) in a cohort aged 35-65, also reported having VMS [6].

In addition to VMS, perimenopausal women often also have issues with mid-sleep wakening, interrupted and non-refreshing sleep [5;7-11] and increased anxiety [8;10;12], although the causal relationships need clarification [11;13]. OMP has been shown to be effective for postmenopausal insomnia [14;15] and to improve sleep in men [16]. Clinical observations suggest it will also help perimenopausal sleep problems. Anxiety is also a common problem for symptomatic perimenopausal women [12;17]. OMP has anxiolytic effects [18] acting through neurotransmitters [19]. In this study we will assess sleep and anxiety (as part of a composite measure of mood) as secondary outcomes, to assess whether they are also improved by the therapeutic use of OMP.

The diagnosis of the "menopausal transition" is divided into early and late based on elevated follicle stimulating hormone (FSH) levels and patterns of menstrual flow. Both major attempts at classification of midlife women's stages, STRAW [20] and ReSTAGE [21], use patterns of menstrual bleeding to delineate late reproductive age (normal FSH levels and no period changes), early menopausal transition increased FSH plus "irregular" cycles) and late menopausal transition (a skipped period, or cycle $\geq$60 d.). These definitions of perimenopause/menopausal transition include only those women whose cycles have become irregular.

Perimenopause extends one year beyond the final menstrual flow [20] and thus differs from the menopausal transition which ends at the final flow. Based on the known hormonal changes and new experiences reported by regularly menstruating midlife women, our research centre extends the bleeding-based definition of perimenopause to also include women ages 35 or older who experience ≥ 3 of the following unexplained changes: (i) new onset of heavy and/or longer flow; (ii) shorter menstrual cycles (< 25 days); (iii) new sore, swollen or lumpy breasts; (iv) new mid-sleep wakening; (v) increased cramps; (vi) onset of night sweats, in particular premenstrually; (vii) new or markedly increased migraine headaches; (viii) new or increased premenstrual mood swings; (ix) weight gain without changes in exercise or eating [22]. Thus, the distinction between **Early Perimenopause** and **Late Perimenopause** is based on menstrual cycle patterns; **Late Perimenopause begins when a woman first goes ≥60 days between spontaneous menstrual bleeding episodes**—all other midlife women with VMS are considered to be in Early Perimenopause.

Although VMS are experienced by menstruating women in perimenopause and by postmenopausal women who no longer menstruate, there are important physiological differences between these two groups [23;24]. **Therapies that work in postmenopause may or may not work in perimenopause** and need to be specifically tested in this population. In perimenopause, hormonal feedback pathways are impaired as part of ovarian aging [24;25]. It is a common misconception that estrogen levels gradually decline across perimenopause. In fact, perimenopausal estrogen levels are higher, on average, than those in younger, premenopausal women [23], because the feedback mechanisms that normally suppress FSH with rising levels of estrogen are disrupted. By contrast, in postmenopause, estrogen levels are low.

Perimenopausal women menstruate, but they have a high rate of anovulatory cycles, and cycles with delayed ovulation and shortened luteal phases [24;26-28] thus the balance between estrogen and progesterone is shifted towards estrogen [27]. Clinically, high estrogen levels present as heavy menstrual flow [29], tender and swollen breasts or increased migraine headaches. Perimenopause may also be a window of risk for endometrial cancer [30]. Exogenous estrogen given as therapy may not suppress a woman's own high perimenopausal estrogen levels [23;25]. Therefore, those estrogen treatments that are effective for VMS in postmenopause may not be as effective in perimenopause, may increase the already elevated endogenous estrogen levels and could cause harm. By contrast with estrogen, progesterone levels are lower in perimenopause than in premenopause.

Although the terms "progestin" and "progesterone" are sometimes used interchangeably, it is important to note that **progestins and progesterone are not the same**. Progestins are, by definition, not normally found in the body, but have two classical uterine progestational effects on the uterus: conversion of the endometrium of an immature rabbit to a secretory state following estrogen priming, and support of rat pregnancy following removal of the ovaries [31]. Other than these two uterine effects, there is no requirement that other actions of a progestin be similar to those of progesterone. Some progestins are derived from androgens, some have androgenic effects, some have anti-androgenic effects, and many differ significantly in structure from progesterone itself. All **progestins share the uterine effects of progesterone**; the **effects on other sites and systems are diverse**.

There is **more research and more clinical experience with the use of estrogens**, and **more with progestins *than with progesterone itself***, in part because of an accident of history and of biology. Following their discoveries in the 1920s and 30s, and unlike estrogen, progesterone was not active when taken by mouth—the quickly synthesized progestins were. Micronization, a comparatively recent innovation, allows progesterone, the same molecule as that secreted by the ovaries, to be used as an oral therapy. Oral micronized progesterone (OMP) was first launched in France in 1980. **In Canada, OMP** (Prometrium®) **was first approved for use in 1995** with USA FDA approval in 1998.

Progestins were added to estrogen therapy in postmenopause to counter the increased endometrial cancer rates of the previously popular estrogen-only therapy; the most commonly used progestin, and the one tested in the Women's Health Initiative, was medroxyprogesterone acetate (MPA). **Most clinicians in North America draw their clinical experience from the addition of MPA to postmenopausal estrogen therapy,** not from the use of MPA or OMP (progesterone) as independent therapy.

Widespread clinical confidence in the cardioprotective and youth-sustaining benefits of estrogen therapy for healthy postmenopausal women was shaken by the results of the large, randomized, placebo-controlled trials of estrogen (for women with a hysterectomy)[32] and Estrogen+Progestin (for women with an intact uterus) of the Women's Health Initiative [33]. Although there is ongoing debate, and a controversial attempt to construct a timing hypothesis to support the benefits of estrogen when used sufficiently early in the sequence of reproductive ageing, it is clear that lifelong use of estrogen therapy for healthy postmenopausal women is no longer recommended. Estrogen therapies are now clearly recommended for the treatment of *symptoms*, not for prevention. Women are advised to use estrogen for VMS but at the lowest possible dose for the shortest possible time, and that the benefits of therapy must be weighed against the potential risks.

Therapeutic recommendations are also drawn from the widespread use of combined hormonal contraceptives for therapy. All oral contraceptives (OC) use progestins, not progesterone (and all available combined OC use *ethinyl* estradiol, not the molecularly identical, 17 βestradiol). Safety profile differences among the progestins in OC remain a controversial and contested area of research. The recent EURAS trial, a large, European, post-marketing surveillance study of the venous thrombosis (VT) risks of OC in premenopausal women confirmed that current formulations cause an approximately three-fold increased risk compared to non-users [34]. The risk of VT also increases with age, body weight (which is notably higher in North America than in Europe), and smoking. Moreover, VMS themselves have been associated with increased cardiovascular risk [35].

<u>The role of progesterone and progestins in perimenopausal and postmenopausal therapy</u>
Both progesterone and progestins have a well-recognized and effective role in the treatment of heavy bleeding [36]. Two older studies [37;38] and a more recent randomized controlled trial [39] from our own group have shown MPA to be an effective therapy for VMS in postmenopausal women. The overwhelming majority of clinical research on the role of progesterone and progestins in perimenopausal and menopausal therapy considers only their protective role against the endometrial cancer that is caused by unopposed estrogen therapy used by a postmenopausal woman with a uterus. A thorough systematic review [40] completed in 2005 (that also found only

the progestin or progesterone studies we describe in this proposal), concluded that "trials of progestin indicate mixed results for the treatment of vasomotor symptoms." The technical report and the NIH consensus statement it informed both called for more research specifically for symptoms in perimenopause, and specifically for more research on progesterone and progestins as therapies [41].

Clinical trials of progestin or progesterone therapy in postmenopause

We have recently (Oct 2009) completed a randomized, masked, placebo-controlled trial of OMP for VMS in healthy postmenopausal women[42]. This is the only trial of OMP for VMS of which we are aware. We found significantly more improvement in those randomized to OMP (Prometrium®, 300 mg at bedtime daily) therapy than to placebo: (52% vs. 22%) improvement in VMS Score, and greater decreases in daily VMS frequency (44% vs. 17%) and severity (38% vs. 19%). Significant therapy by baseline interactions indicated that those who had more frequent/intense VMS at baseline showed greater treatment benefits from progesterone compared with placebo, for both VMS Score and VMS Frequency. This analysis considered all randomized women for whom we had daily diary records of VMS (n=127); for 13 of these, we used last observation carried forward to impute the final score.

Considerable RCT evidence is available showing the effectiveness of medroxyprogesterone (MPA), the most biochemically similar progestin to OMP, either orally [37;38;43;44] or as a depo-injection [43;45] for the treatment of VMS. Furthermore, a parallel double-masked 1-yr trial (begun in the 1980s when these were the dominant hormonal therapies) of conjugated equine estrogen (Premarin®, 0.6 mg/d) compared with MPA (Provera®, 10 mg/d) found equivalently effective control of the expected increase in VMS following bilateral ovariectomy in premenopausal women [39]. The three published trials of transdermal progesterone cream (Pcream) for VMS in menopausal women showed contradictory results—one with 20 mg/d over one year showed significant improvement [46] while a 12-week trial of 32 mg/d Pcream showed no significant effect [47], and a dose-response trial tended to show benefit at the highest dose [48].

Neither our searches nor those of others recently reviewing the literature [40] have uncovered any further controlled clinical trials investigating progestins or progesterone as therapy for postmenopausal VMS.

Clinical trials of progestin or progesterone therapy for VMS in perimenopause

We have been unable to find any such trials.

Clinical trials of other therapies for VMS in perimenopause

The most common recommendations for perimenopausal symptoms are to use the estrogen-based therapies that are the gold standard for postmenopausal women, or to use OC [49]. Neither recommendation is supported by evidence from clinical trials with perimenopausal women. The only clinical trial of OC (Minestrin, 20 mcg ethinyl estradiol with 1 mg norethindrone acetate) for perimenopausal symptoms [50] enrolled 134 women aged 40-55 who were menstruating (details not provided), with FSH levels <40 mIU/ml, who were "experiencing perimenopausal signs and symptoms" and without contraindications to combined OC. Women were randomized to take OC or identical placebo for 6 28-day cycles (168 days) with a standard 21/7 pattern of active and placebo pills. The study had multiple endpoints, one of which was VMS; 65% of the women had one or more hot flush during the study and were included in that analysis. For a

VMS therapy study, the rate of hot flushes was very low. The average daily count was 0.45 for placebo and 0.24 for active therapy, and the range was from 0.1 to 2.1 hot flushes per day. The difference between placebo and active therapy was not statistically significant, nor was the magnitude decrease observed (0.2, or roughly one fewer hot flush per 5 days) likely to be perceptible to the women or clinically relevant [50]. The other trial of OC in perimenopause provided incomplete description of the methods and its methodological flaws limit data interpretation [51]. **While it is possible that hot flushes can be effectively treated with oral contraceptives, this has yet to be established in a clinical trial.**

Recently a clinical trial of a rhubarb-like herb (ERr-731) with 110 perimenopausal women found significantly better treatment of VMS than with placebo [52]. This formulation, however, is not currently available in Canada and the study methodology was importantly lacking [53].

In summary, progesterone is a likely candidate therapy for VMS in perimenopausal women because:

1. It is an effective therapy for VMS in healthy postmenopausal women within 10 years of their final menstrual flow [54];
2. It counters the known endometrial risks of elevated and unopposed endogenous estrogen, and is effective therapy for abnormal and heavy bleeding which is common in perimenopause; and
3. The sedative effects of OMP, when taken at bedtime, have additional benefits for improving sleep [14], and may reduce anxiety [18], both of which are frequent problems for symptomatic women in perimenopause.

This study will be the first to specifically address the treatment of VMS in perimenopausal women, and, if successful, will improve clinical care. The availability of effective therapy will ease the burden on health care utilization, improve the health and lives of perimenopausal women who are symptomatic because of VMS, and may also improve their associated perimenopausal bone loss [55] and increased cardiovascular risks [35].

1.2 Principal research question

Research Question: Is progesterone (OMP) an effective treatment for night sweats and hot flushes in perimenopausal women?

1. Is daily OMP therapy (300 mg, taken before sleep) an effective therapy for hot flushes and night sweats (vasomotor symptoms, VMS) in Early and Late Perimenopause?
2. Does OMP therapy improve other perimenopausal symptoms, specifically sleep disturbances and anxiety?

1.3 Why a trial is needed now

In addition to the reasons given for the relevance of this trial (section 1.1), clinical trial data from the Women's Health Initiative [32;33] have created great interest in alternatives to estrogen treatment. The post-war "baby boom" generation is now passing through their perimenopausal years and thus there is a large demographic (22% of all Canadian women) and approximately 20% of these will be sufficiently symptomatic to seek medical treatment.

We have recently completed a trial of OMP for postmenopausal VMS [42;54], showing that significantly greater improvement in those randomized to progesterone than placebo. This trial provides proof of principle that OMP is effective VMS therapy. However, OMP remains to be

tested in perimenopausal women. Further, the investigators have the expertise for this new VMS trial in perimenopause. For all of these reasons, this is an ideal time for this important trial.

1.4 Systematic reviews of treatment of VMS

A meta-analysis of randomized controlled trials of estrogen or estrogen and progestin for VMS was unable to find any trials that studied VMS only in perimenopausal women [56]. Clinical trials for VMS in perimenopause are few. Recently a rhubarb extract was shown to be more effective than placebo, but this has not been standardized and is unavailable in North America. There are two trials of OC in perimenopause. In one case OC was not better than placebo [50], and in the other case incomplete description of the methods and methodological flaws limit data interpretation [51]. Medroxyprogesterone, which is a progestin that is most biochemically similar to progesterone of any other available in North America, has repeatedly been shown to be effective for VMS [37;38] and equally effective as estrogen [39]. The results of three trials of transdermal progesterone cream were inconsistent, with one showing efficacy and the others not [46-48].

There is an extensive systematic review of the literature on hormonal therapies in postmenopausal and perimenopausal women [40] that was prepared following the Women's Health Initiative clinical trial results to support a 2005 NIH Consensus conference [41]. This review and the summary documents from the consensus statement summarize the same few studies on progestins and progesterone that we have found, and call for more research in this area. Systematic searches of the clinical trial registries and of PubMed have not found any further relevant research.

1.5 Use of trial results

The trial results will be published in peer-reviewed journals, and in articles reviewing the options for perimenopausal VMS in general medical journals specifically for family practice physicians. A variety of media will be used to communicate our trial results such that these results will be readily accessible and available to the medical and also the women's health communities. In addition, our results will be presented on the Centre for Menstrual Cycle and Ovulation Research (CeMCOR) website (www.cemcor.ubc.ca) to provide information on treatment options for treating severe VMS. Our efforts to inform women will use the CeMCOR website, print and other media, and free public lectures as well other women's health on-line resources (BC Centres of Excellence for Women and Health, Women's Health Research Institute, Society for Menstrual Cycle Research blog, etc.).

1.6 Potential risks to the safety of participants involved in the trial.

We do not believe that there are significant risks to participants involved in this trial. There were no serious adverse events related to OMP in our recently completed trial with 127 postmenopausal women [54]. In studies of combined therapy, it is common to describe estrogen positively and ascribe negative side effects to progestins or progesterone [57;58]. There are remarkably few placebo-controlled trials on the safety of OMP alone; those that are available show positive rather than negative effects [14;18]. Both progesterone and synthetic progestins are predominantly used to prevent endometrial cancer in postmenopausal women treated with estrogen therapy, and drug prescription databases list the same adverse effects for progesterone as they do for estrogen therapy. It is worth noting that progestin-only OC carry a clear disclaimer that combined estrogen-progestin OC side effects (especially thromboembolic disease) do not

apply to progestin-only formulations; this distinction appears to not have been sought for progestins or OMP prescribed for non-contraceptive purposes.

No convincing evidence suggests that OMP alone (without estrogen) causes thromboembolism, breast cancer, heart disease, migraine headaches, fluid retention or depression, although large, long-term safety studies are not available. This is a short-term (3 month) therapy trial and we will carefully document adverse events, particularly those that have been attributed to progesterone.

Women assessed as having high risk for breast cancer (ie first degree relative with breast cancer or known/suspected history of breast cancer) will be required to have a normal screening mammogram and clinical breast examination within 12 months of study enrollment.

Women who are breastfeeding will be excluded.

Although fertility is reduced in perimenopause, unplanned conception remains a possibility. There are no teratogenic effects of progesterone during pregnancy, however [59]. Sexually active women wanting to conceive will be excluded; those not planning pregnancy will be strongly advised to use appropriate methods of non-hormonal birth control (barrier methods such as condoms/diaphragm + vaginal spermicide) for the duration of the study.

The proposed therapy differs slightly from that used in clinical practice. When progesterone is prescribed for symptomatic Early Perimenopausal women, the PI typically recommends it be taken cyclically (days 14-27 of the regular menstrual cycle or 14 days on and 14 off for those with irregular cycles). Clinical practice for women in Late Perimenopause is to prescribe progesterone daily because periods are not expected to be regular. Because this trial is treating women in both Early and Late Perimenopause, and cyclic OMP would likely be ineffective in Late Perimenopause, we will use *daily* OMP. Because of the disturbed perimenopausal hypothalamic-pituitary-ovarian feedback loops, daily OMP should reduce but not eliminate flow, and will be unlikely to suppress endogenous estradiol levels in those in Early Perimenopause whose flow has been regular or slightly irregular.

Late Perimenopausal bone loss is almost universal (almost 2% loss a year by meta-analysis of spine dual energy X-ray absorptiometry [23;60]), therefore we will provide all participants with the "ABC's of Midlife Osteoporosis Prevention" handout (from www.cemcor.ubc.ca) and advise they follow its instructions.

The dose of OMP, 300 mg/day, is one that, although larger than the typical 100-mg postmenopausal dose, keeps the blood level of progesterone above the luteal phase threshold for 24 hours, given that, because of drowsiness effects, it must be dosed only at bedtime [61].

OMP causes drowsiness in some women, and so should be taken just before bed. This timing is predominantly so that the soporific effects of OMP occur during sleep, which has two benefits: (i) drowsiness happens during sleep and does not interfere with daytime functioning; (ii) it can decrease sleep latency, increase early REM sleep and decrease sleep fragmentation [14], all of which are benefits in this population. The precise timing is not important, and usual variability in bedtimes will not be an issue.

2. The Trial

2.1 Trial design

This is a double-masked, placebo-controlled 28-day (4-week) baseline, 84-day (12-week) experimental trial, enrolling 175 women and stratifying random therapy assignment by Early or Late Perimenopause.

2.2 Trial interventions

The proposed trial intervention is OMP, 300 mg/day (Experimental) or matching placebo (Control), each taken as three capsules daily before sleep. This is important because OMP should not be taken during waking hours because of its soporific effects [14]. The dose of 300 mg of OMP is a physiological one that maintains the serum progesterone at or above the luteal (normal post-ovulatory) threshold for 24 hours [61].

Placebo-control of trials are required for VMS therapy because of the well-known response to placebo treatment, estimated by meta-analysis of RCT studies as 50.8% improvement (95% CI 41.7-58.5) [56]. Postmenopausal women randomized to placebo in our randomized trial showed a 22% reduction in VMS Score (daytime VMS number X intensity plus nighttime VMS number X intensity) from baseline [54]. Also, there are no effective therapies to use for an active comparison. There is an additional reason to include a placebo control for a VMS trial with perimenopausal women, because the natural history is for hot flushes to be variable and to increase over time to a maximum during the final year without flow [3;9].

2.3 Allocation of participants within the trial

Random allocation will be stratified by phase of perimenopause (Early, <60 days cycle length, versus Late, having had at least one ≥60 day long menstrual cycle). Two lists of random numbers will be computer-generated by a statistician not associated directly with the study. Permuted blocks of size 10 will be used. A research pharmacist will access appropriate (Early or Late Perimenopause) lists from this computer webpage to determine whether to dispense Experimental or Control therapy.

2.4 Protecting against bias

Neither participants nor research staff (including the research coordinator, and anyone directly related to the trial) will know who received Experimental or Control therapies. The only person directly interacting with participants who will know the therapy assignment will be the research pharmacist. Progesterone and placebo will be provided as white coloured, round capsules, identical except for the active ingredient. Investigators will remain masked until all participants have completed the study and the data have been entered, cleaned and checked.

As each participant completes her participation, the research pharmacist will provide her with a letter disclosing her therapy assignment, with instructions to not disclose it to the researchers. (Although therapy assignment is conventionally withheld from participants until study completion, we feel that participants need this information to make informed choices about active therapy following their participation and before the end of the study. By providing women with copies of their own diary data and their therapy group assignment, we allow them, in a timely manner, to directly benefit from study participation. We have found this an additional incentive for study participation.)

Besins Healthcare, providers of drug and placebo, will have no role in the design, conduct, analysis or publication of the study.

2.5 Inclusion/exclusion criteria

To make the study as widely generalizable as possible, the study inclusions are broad and there are minimal exclusions:

Inclusion:

- ≥35 to ≤58 years of age
- At least4 VMS per day on average, for at least two weeks of every four-weeks, or at least 56 over a four-week period. In addition, women should report having VMS that of moderate or severe rather than of mild intensity. Women reporting fewer VMS than this, but who report night sweats that awaken them from sleep on two or more nights per week will also be included, because we believe that VMS that disturb sleep are clinically important.
- Perimenopausal status either based on irregularity of menstrual periods, or by onset of new perimenopausal symptoms in women with regular periods [22] (as described earlier).
- At least one menstrual period within 12 months of study enrollment
- Ability and willingness to complete the Daily Perimenopausal Hot Flush Calendar recording instrument.
- Ability to understand, speak, read and write English.
- Women who are at high risk for breast cancer (ie first degree relative with breast cancer, known/suspected history of breast cancer) will be required to have a normal mammogram and clinical breast examination within 12 months of study enrollment.

Exclusion:

- VMS without perimenopausal etiology
- Women who have had a hysterectomy, ± ovariectomy
- Peanut allergy (because peanut oil is used in the progesterone formulation)
- Current or recent (within 6-mo of study enrollment) use of hormonal therapies (estrogen, progesterone, hormonal contraceptives, hormonal fertility treatments), or plans to initiate use during the study period. Two exceptions will be made. The first is women using a progestin-releasing intrauterine device (IUD) will not be excluded as it is felt that the level of hormone released will not have an effect on VMS. The second is women taking very low-dose transdermal progesterone therapies who have VMS and meet inclusion criteria will be considered for inclusion on a case-by-case basis. If enrolled, they will be required to continue and document use of this very low-dose hormone therapy throughout the entire trial.
- Planned pregnancy or fertility treatment during the study period
- Women who are breastfeeding
- Participants with a score of ≥ 15 on the Personal Health Questionnaire (PHQ-9) will be assessed on a case-by-case basis. Women assessed as needing further investigation and/or treatment for depression will be excluded.

2.6 Duration of the experimental period

The treatment period is 12-weeks (84 days). This is conventional for VMS treatment trials, and is recommended by the FDA for VMS studies for postmenopausal women [62].

2.7 Frequency and duration of participant follow up

Screening Study enquirers will be screened initially by telephone.

Subsequent study visits will occur in-person or through remote participation; this differentiation will be recorded in the study database. Procedures are identical for both types of participation except that communication for remote participation will be through web-conference (Skype), telephone, email or mail. Participants returning study documents and medication via mail will be provided with postage-paid envelopes. Faxes will be received into confidential fax machines.

Initial Visit

Women will review the consent form sent by email, fax or mail. Eligible women who remain interested will be seen in person, sign informed consent, receive a fully executed copy of the consent, complete questionnaires and be taught to keep the Daily Perimenopause Hot Flush Calendar ('the Calendar.') Instructions for completing the Calendar will be included on the Calendar form. With remote participation, verbal consent will be obtained, the participant will email, fax, mail the signed consent. As measures of good health practice, breast self-examination will be taught, women will be encouraged to perform this monthly and women will be provided with a handout on osteoporosis prevention.

Randomization Visit (one month after initial visit)

The Calendar data will be assessed for completeness and clarity. Participants will complete some health questionnaires. Based on self-report of maximum menstrual cycle length during the previous year, women will be stratified to Early (<60 days) versus Late Perimenopause ($\geq$60 days). This information will be provided with a prescription to the study pharmacy so they can be randomized to Experimental or Control therapy. With remote participation the research coordinator will obtain study medication on the participant's behalf and send it to the participant via courier.

Monthly follow-up while on study treatment

During study treatment period, women will be contacted by telephone or e-mail monthly to assess their progress, monitor for safety and to answer any of their questions.

Final Visit

Women will return completed Calendar forms, complete questionnaires, return any remaining study medication. Returned pills will be counted and/or Calendar recording will be reviewed, to assess adherence and ensure drug accountability. The final questionnaire may be emailed/faxed/mailed to the participant for completion the day following last dose of study treatment, in the event the final visit cannot be scheduled for this date.

2.8 Primary and secondary outcome measures

The primary outcome will be assessed from prospective records using the Daily Perimenopause Hot Flush Calendar. The Calendar is a one-page chart with a vertical column for each day of the month that includes flow, sleep problems and anxiety as well as VMS (attached). Items are rated

on 5-point scales or as counts, as appropriate. Daily VMS frequency and severity are recorded separately for hot flushes during the individual's waking or work day and night sweats that occur during sleep. Uniformity of training will be addressed through standardized verbal and written instructions.

PRIMARY OUTCOMES

1. Vasomotor Symptoms (VMS) – VMS Score, computed from prospective daily Calendar ratings of night sweat frequency and severity and hot flush frequency and severity as [64]:
   Daily VMS Score = (# night sweats) x (severity) **+** (# hot flushes) x (severity) and summarized as a daily average during the final 28 days of therapy with average run-in scores as a covariate. This composite score has the advantage that it includes both number and intensity during the waking day and during sleep. However, this score assumes that two moderate episodes are equivalent to a single very intense episode, which may or may not be the case.
   Subgroup analysis for those with frequent and severe VMS: To complement this analysis, we will do a subgroup analysis of the number and VMS Score for those with more frequent (≥7/d and moderate to severe episodes of intensity ≥2) at baseline.
2. Frequency and Severity (0-4) of VMS, evaluated from prospective daily Calendar ratings as a daily average during the final 28 days of therapy with average run-in scores as covariates.

SECONDARY OUTCOME:

3. Daily prospective ratings of Sleep Problems (0-4) and Anxiety (0-4) evaluated from prospective Calendar ratings as a daily average during the final 28 days of therapy with average run-in scores as covariates.

As additional assessments of health, participants will complete the following questionnaires:

Personal Health Questionnaire – 9 (PHQ-9) is a standardized questionnaire administered as a screening tool for depression [66]. A score of 15 or higher represents moderately severe depression and is the point at which treatment is recommended. Women with PHQ-9 scores ≥ 15 will be assessed on a case-by-case basis. Women will be excluded if assessed as needing treatment and/or further investigation for depression. Also, region-specific contact information for mental health resources will be provided. Women suspected of being suicidal will be advised to go to the nearest emergency department and emergency services will be deployed as appropriate. The PHQ-9 will be completed at the randomization and final visits.

CeMCOR Perimenopause Interference Questionnaire (attached).
We have recently developed and validated this two-item, self-administered visual analog scale to assess the extent to which the body and mood changes of perimenopause interfere with a woman's usual activities. The two items are averaged to provide a single 100-point score. In a recent validation study (Hitchcock & Prior, unpublished MS), we showed fair test-retest repeatability over a 1-2 month period (R=0.51, n=42), as well as a good correlation with the Vitality Scale of the SF-36 HRQoL instrument (R=0.59, n=62). Using the interpersonal comparison method of Redelmeier [69], we estimate that the minimal important difference in the CeMCOR-PIQ is 17. The CeMCOR-PIQ will be completed at the initial, randomization and final visits.

2.9 Measurement of outcome measures at follow up

The study timeline for each subject is shown on the following page. Women will complete the Diary or Calendar throughout the study. Questionnaires will be completed at the initial, randomization and final visits.

2.10 Relevance to health care service

No formal health economic analysis is planned. The costs of the proposed intervention are modest (as compared with, e.g., surgery) and a complete health economic analysis would require data collection well beyond the scope of the study.

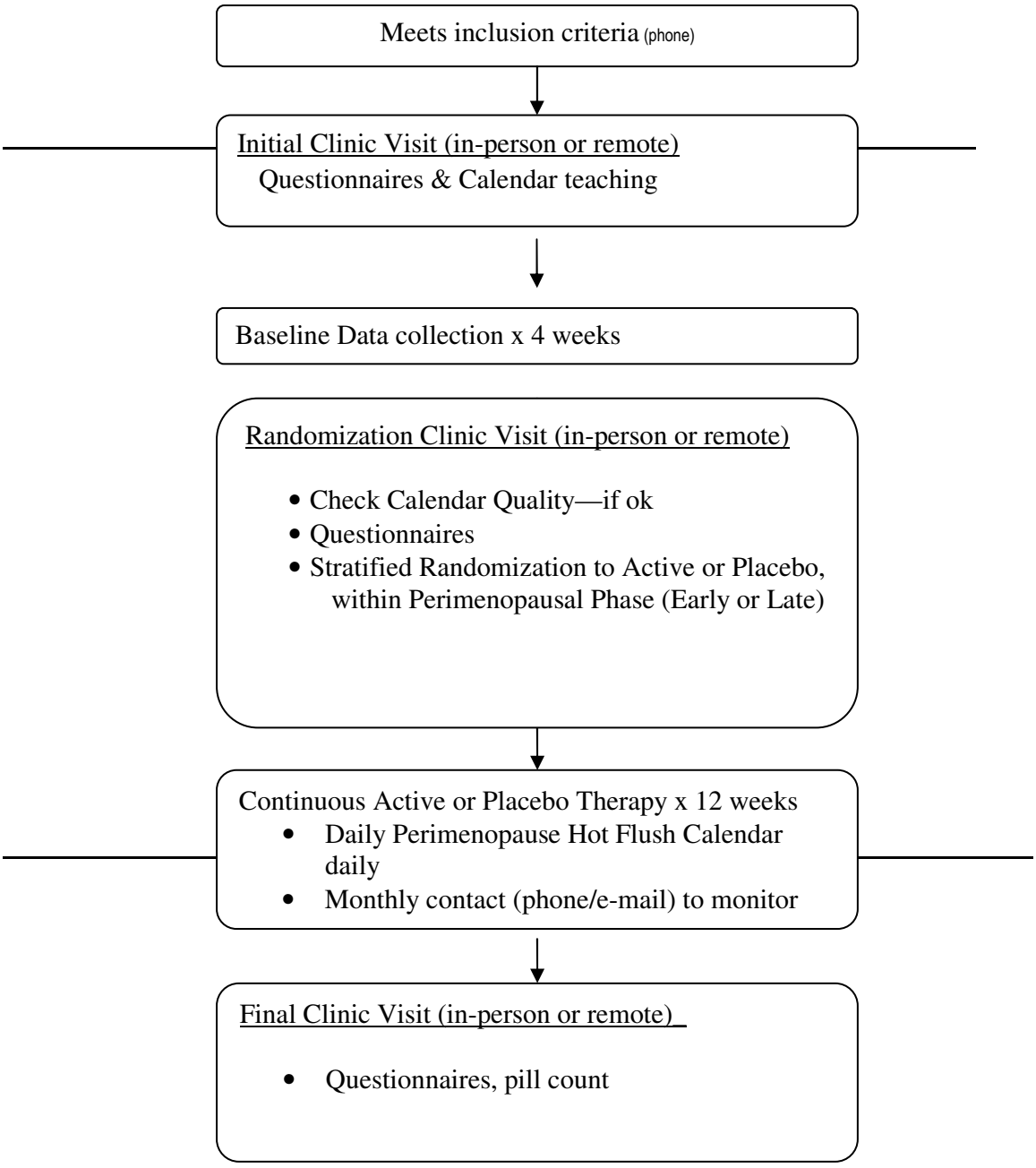
2.11 Sample size

The **proposed sample size is 175 women**, to be stratified into Early and Late Perimenopause and randomized equally to active therapy or placebo. Previous analysis of similar VMS Score data from menopausal breast cancer therapy studies [64] concluded that a VMS Score difference of 3 is clinically important, which supports our recent estimate of 2.7 for the minimal important difference in perimenopausal women using the interpersonal assessment methods of Redelmeier [69] (Hitchcock & Prior, unpublished MS). This corresponds to an effect size of 0.58 [64]. We anticipate more VMS variability in perimenopause than in postmenopause, and thus a smaller effect size. The sample size of 175 reflects an anticipated discontinuation rate of 20% (as in our past progesterone trial for VMS in postmenopausal women), and an effect size of 0.48 (revised to allow for 20% greater SD in perimenopausal women above that in postmenopause), an alpha of 0.05 using a two-tailed test and having a power of 0.80 to detect a significant difference between two groups (calculations using GPower3)[73].

2.12 Recruitment—rate, organization, evidence it is achievable

Given our previous recruitment success, we anticipate that many perimenopausal women will be interested in participating. Each woman's participation will take 112 days (timeline below).

Figure 3: Flow of Participants through the Trial.



We plan a three-year continuous recruitment period, with a gradual increase in recruitment during this time as word-of-mouth increases (see **Gantt chart** in appendices). We will allow extension of this recruitment period if enrollment targets are not met and funds allow. We project enrollments of 20, 60, 75 and 20 women during the four years of the study (Year 1 includes 6 months of recruitment; Year 4 includes two months of recruitment and 4 months to allow completion of the study by the last participants) with an anticipated six women enquiring about participation for each eligible and enrolled participant (based on our pilot research experience).

Our past recruitment experience has shown that broadcast emails at a local health authority, posting notices on library and community boards, advertising on the CeMCOR web page and newsletter, and free public lectures on perimenopause will all be effective. We will, of necessity, include more internet and social media-based as well as cross-Canada women's health and perimenopausal contacts to aid recruitment. For our recently completed randomized trial for postmenopausal women, we enrolled 178 postmenopausal women with VMS, using more stringent screening conditions (e.g., non-smoking, normal body weight, no history of heart disease, normal measured fasting glucose and lipids and ECG). ***Many were perimenopausal who sought information but were ineligible for that study***, further illustrating the demand for a perimenopausal VMS study.

CeMCOR has a history of excellent recruitment: 120 women contacted us the first day of a study needing 100 women; 610 premenopausal women not on OC were enrolled and studied for one menstrual cycle within a 16-month time period; and 114 women with PCOS enrolled and were studied within 8 months. Thus, recruitment of the required 175 women is feasible given the geographical and women's media reach of investigators and collaborators and use of internet and social media recruitment strategies.

Approximately 22% of all women in the Metro Vancouver region are in perimenopause and, based on a recent large epidemiological survey, approximately 9% of this population will have severe VMS [1]. Remote participation will offer the opportunity for women living outside the Metro Vancouver area to participate as well. There is a large population of women looking for answers and likely to enroll. CeMCOR and the PI have a history of excellent study recruitment rates, supported by a popular website for laywomen (www.cemcor.ubc.ca) and the publication of several books, including an award-winning book about perimenopause, Estrogen's Storm Season—stories of perimenopause [10].

2.13 Compliance/Adherence

The research coordinator will be systematically making contact with and ensuring the well being of each participant monthly during the experimental phase. If adherence or record-keeping problems were anticipated, this should decrease those risks.

A review of adherence in our progesterone for postmenopausal VMS study showed that 98.8% of women used 80% or more of their pills, and the average was 96%. The single individual with poor adherence (42%) discussed her difficulty with the coordinator. Part of our research practice is to reassure women that we all occasionally miss pills, and to record this. This limits the perception that we expect perfect adherence, decreases participant anxiety, and leads to openness about pill taking. Serum progesterone levels could, potentially, be used to confirm adherence.

However, in perimenopause this measurement would be confounded by menstrual cycle timing and progesterone production following ovulation. It is a greater burden to participants and research staff than warranted to obtain a timed progesterone blood sample (at a particular phase of the menstrual cycle) in perimenopause, a life phase characterized by unpredictable and sometimes very long menstrual cycles.

Recent reports of the unreliability of paper-based daily diary methods have come from studies funded by companies who market hand-held electronic record systems [74]. Electronic diary systems are expensive and carry their own issues of training and usability. However, we will be open to developing one should the opportunity arise and funds allow. Our experience over more than 25 years of using daily diary instruments in clinical and research practice is that women are motivated to keep accurate diaries. They often report that the diary-keeping provides valuable insights and helps them understand their new and confusing experiences. The information women gain about their own experience through keeping the Diary or Calendar is, itself, rewarding and encourages study continuation. Our study coordinator emphasizes that the Calendar is important as our primary tool for measuring VMS, and suggests that the woman use it to understand and learn more about herself.

A routine Calendar check after the baseline month and before randomization further ensures data quality. Should there be a problem with diary quality, the research coordinator will individually review items, offer supportive corrective feedback and will ask that the participant keep her record for a further baseline month. All of these strategies are likely to lead to excellent Diary or Calendar quality.

2.14 Likely rate of loss to follow up

We anticipate that 20-25% of women will discontinue the study following randomization. This figure is based on our experience of those who did not complete our progesterone for postmenopausal VMS study (not including secondary exclusions for abnormal lipids or ECG) in our similar-length trial. The higher figure was for drop-outs during a more demanding (one cycle of daily urinary hormone collection) pilot observational study of perimenopausal VMS.

2.15 How many centres will be involved?

This is a single-centre study by CeMCOR at Vancouver Coastal Health Research Institute. Given the required sample size, broad inclusion criteria and lack of need for in-person visits, it is feasible to complete this study as a single centre trial; the methodologies and quality assurance measures are all in place. However, given our unexpected recruitment shortfall we have converted it to a single centre Canada-wide trial with remote or in-person options even for locally residing participants.

2.16 Statistical analysis

The analysis will use analysis of covariance (ANCOVA) of the final outcome variable by therapy assignment, phase of perimenopause (Early/Late) and the interaction of therapy with phase, with baseline outcome variable as a covariate [75]. The interaction term will assess the possibility that the response to therapy differs between those in Early and Late Perimenopause. For Daily Perimenopause Diary or Calendar VMS data, two 28-day (4-week) averages will be compared: immediately prior to therapy assignment and the final 4-weeks of the treatment phase. For questionnaires, the scores from pre-randomization and final visits will be used. The

assumptions of parametric analysis will be checked, and data will be either transformed prior to analysis or analyzed non-parametrically as required.

The primary analysis will be *intent to treat* including all women randomized and taking at least one dose of the experimental/placebo therapies with data carried forward. For practical reasons, only those with at least 14 days of Daily Perimenopause Diary or Calendar data will be included in any diary-based outcome measures (one week of baseline and one week of therapy).

2.17 Frequency of analyses

There will be a single primary analysis when all data are entered into a database and checked for completeness and accuracy. However, our sample size calculations were based on the assumption that the SD for within-woman change during perimenopause will be 20% greater than that in menopause. Through the Data Safety and Monitoring Committee, an interim analysis when we have sufficient data for comprehensive assessment, will confirm whether this assumption was accurate; if necessary, we will increase our enrollment target to ensure we have 80% power.

2.18 Subgroup analysis

We plan to do a *sensitivity analysis* of the results for those women whose pill counts show at least 80% adherence for at least 60 days of experimental treatment.

We will also perform a *subgroup analysis* for those women who meet the FDA recommended (postmenopausal) threshold for frequent, moderate-severe VMS (>50 VMS/wk of $\geq$2 intensity).

Should our enrollment of women identifying as non-white/non-Caucasian allow it, we will assess the role of ethnicity in the effectiveness of progesterone therapy for VMS.

Participants in clinical trials may become unmasked to therapy assignment as a result of their experiences. Because, in our previous trial, women used lack of drowsiness or improved sleep to decide they were on placebo, we have explicitly stated in the consent that not all women on progesterone experience sleep changes. To address the role of expectation on the outcomes, at the final visit we will ask women whether they believe that they were randomized to the Experimental or Control therapy. This information will be used to examine the potential role of expectation on the VMS outcome.

2.19 Pilot data

The experimental design is exactly parallel to a recently completed study. In that study, we enrolled 178 healthy VMS treatment-seeking postmenopausal women (1-10 years beyond their last menstrual period) into a randomized, double blind, placebo-controlled trial of daily OMP (300 mg). Secondary cardiovascular exclusions do not apply to the proposed perimenopausal study, therefore we have incorporated the observed rate of women discontinuing after randomization (20%) into our power analysis.

We also have studied 27 menstruating early perimenopausal women aged 35-50 with regular menstrual cycles and night sweats in a four-cycle observational study to pilot and validate some new questionnaires and to confirm our sample size calculations. Of these, 20 completed the entire trial (including a 1.5 cycle daily first morning urine collection). Based on this experience, we anticipate that we will enroll one woman out of each six contacts, and that 20% of enrolled

women will discontinue before study completion. Women appear most likely to discontinue prior to randomization.

3. Trial Management

3.1 Arrangements for day-to-day management of the trial

A research coordinator for the study will handle the day-to-day tasks of responding to potential participants who enquire, assessing eligibility, teaching them how to complete the Calendar and interviewing them. The research coordinator will be under the direct supervision of the principal investigator and will meet with her regularly at no less than two week intervals.

When participants have completed the baseline assessment and their symptoms meet randomization criteria, they will be given a prescription for masked study medication which also has information on their Early or Late Perimenopause status. The pharmacist will access the web-based treatment allocation programme to obtain the next randomly selected allocation (see section 2.3 for details), and dispense either OMP or placebo to the participant. For remote participants, the research coordinator will go the study pharmacy on the participant's behalf and send the medication by courier.

Should there be a medical need to determine the therapy assignment for a participant during the study, Dr. Michelle Fung, who is not directly involved with participants, will address any relevant clinical concerns. Dr. Caroline Ferris or Dr. Sandra Sirrs who are also not directly involved with participants, will act as back-up in the event Dr. Fung is unavailable.

3.2 What is the role of each principal investigator and co-investigator?

Jerilynn C. Prior BA MD FRCPC: Principal Investigator. Dr. Prior has over 30 years of clinical research experience, including designing and conducting four previously published RCT, and is a full time UBC Professor of Endocrinology. Dr. Prior is responsible for the conception, justification, design, conduct and publication/communication/translation of trial results as well as direct supervision of the research coordinator and all other personnel.

Andrea Cameron RN BScN: Co-Investigator. Ms. Cameron will be the research coordinator for the trial and contribute to decisions regarding trial design, management and conduct as well as being involved in the interpretation and publication of results.

Michelle Fung MHSc MD FRCPC: Co-Investigator. Dr. Fung is a Clinical Assistant Professor of Endocrinology with previous research design and implementation training and is active in islet cell transplantation research at VCHRI. Dr. Fung works at the Osteoporosis Clinic and has her own practice from which she can inform potential participants of the study. She will not be directly involved in participant management and thus could handle unexpected adverse events, including breaking the code, if necessary.

Christine L. Hitchcock MA, PhD: Co-Investigator. Dr. Hitchcock has clinical research experience and has worked with Dr. Prior for over 12 years. She has contributed importantly to experimental design and development of study materials. Since she is no longer in the region, depending on her continued input she will participate in the final analysis and interpretation/ publication of the data or not.

Shirin Kalyan PhD: Co-Investigator. Dr. Kalyan is a UBC Research Associate after a three-year post-doctoral clinical research fellowship with Drs. Prior and Hitchcock. Dr. Kalyan, now a Junior Research Fellow in the prestigious von Humboldt programme in Germany but is expected to return to a UBC position in 2014. She will assist in later trial management, and preparation of final manuscripts and knowledge translation.

Sandra Sirrs MD FRCPC: Co-Investigator. Dr. Sirrs is a seasoned endocrinology clinician who will provide support and advice in the conduct of the trial, act as back-up physician for breaking the code and assist with the interpretation and dissemination of the results.

Patricia Janssen PhD: Co-Investigator. Dr. Janssen, a Professor in SPPH at UBC with a clinical background in nursing and midwifery, has designed, funded and conducted practical clinical trials in women's health and worked with Dr. Prior for >6 yr. Dr. Janssen will review the experimental design, and assist in research interpretation and publication.

Joel Singer, PhD: Co-Investigator. Dr. Singer is a professor in the SPPH at UBC. He will be involved with important decisions regarding study management, interpretation and analysis of data and publication of results.

Caroline Ferris MD: Collaborator. Dr. Ferris is a family practitioner and founder of the Morgan Creek Women's Health Clinic in a southeastern suburb of Vancouver. She is also working with the Fraser Health Authority, has previously worked with Dr. Prior and will be a primary/family physician consultant for the study, contact for the family physician community, and will be active in recruitment and knowledge translation. She is also a back-up physician for breaking the code.

Elana Brief PhD: Collaborator. Dr. Brief is a UBC Research Associate in Physics, and active in promoting women's health research in BC through several leadership roles. She will also be assisting with recruitment and knowledge translation.

3.3 Trial Steering Committee and Data Safety and Monitoring Committees

All co-investigators will form the **Trial Steering Committee**—this group will meet as needed during and following the trial until the results are published and disseminated.

A **Data Safety Monitoring Committee** (DSMC) will consist of three members including a methodologist/statistician (Chair—Dr. Hubert Wong, Professor SPPH at UBC) and two clinician-scientists with clinical trials experience and expertise in perimenopause and VMS (Drs. Nanette Santoro, Chair of Obstetrics and Gynecology at University of Colorado in Denver and Leora Swartzman, Associate Professor of Psychology at University of Western Ontario in London, Ontario). The DSMC will meet every six months during the trial.

4. Assessment of Safety

An **Adverse Event** will be defined as follows:
Any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

A **Serious Adverse Event** will be defined as follows:
A serious adverse event (experience) or reaction is any untoward medical

occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect .

Adverse events will be assessed throughout study participation through direct questioning of study participants, by specific study-end questionnaires and will all be followed to resolution.

All serious adverse events will be assessed by the principal investigator, reported to the DSMC and the local research ethics board, and be followed to resolution. Adverse Drug Reactions will be reported to Health Canada per applicable regulatory guidelines. For study data purposes, period of capture for serious adverse events and adverse drug reactions will be from first, up to and including last day of study treatment.

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a place of mind
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18 November 2018

To whom it may concern:

Re: Randomized Controlled Trial of Progesterone for Perimenopausal Vasomotor Symptoms

As Chair of the Clinical Research Ethics Board (CREB) at the University of British Columbia (UBC) that has overseen and approved the Canadian Institutes for Health Research-funded Randomized Controlled Trial of Progesterone for Perimenopausal Vasomotor Symptoms (VMS) since it began in 2011, I have reviewed the posted protocol, which was the latest one approved by CREB and the evidence that it has some inadvertent clerical omissions. I have also reviewed the proposed Amendments to this protocol.

The protocol omissions include this study's Data Safety and Monitoring Committee decision (and details about the blinded analysis leading to it) that led to the official increase in sample size. Another was that the DSMC mandated addition of the Personal Health Questionnaire-9 (PHQ-9) to screen for depression. The investigators then decided (and CREB approved) administration of the PHQ-9 also at the study end. However, the analysis of PHQ-9 was inadvertently not listed as a secondary outcome. And finally other instruments were included in the study initially for administration at the randomization and the final study visits, were approved by CREB, were partially described in the protocol but not were listed as secondary outcomes including: a likert-type assessment of "Women's Perception of Change" (related to daytime hot flushes and night sweats, flow and sleep) and the CeMCOR Perimenopause Interference Questionnaire (CeMCOR PIQ).

Although it is unusual to amend a RCT protocol once the database has been locked and statistical analysis has occurred, these amendments to the protocol are important, and they will allow the outcomes of approved, collected instruments to contribute to the scientific literature. To collect data that, for inadvertent clerical reasons cannot be evaluated and reported, would be unethical given the overall "contract" that participants make with investigators and institutions. Participants expect that what they have contributed will add to Knowledge with an expectation of providing benefit for Society or Science.

For these reasons, I approve uploading of Amendments dated November 9, 2018 to the 2014 posted protocol.

All the best,

Stephen

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These amendments are to the Progesterone for Perimenopausal VMS Protocol version 7; 12 June 2014; 09 November 2018

Amendment #1 (2.1 Trial Design):

This enrolment goal was changed to 245 women based on the blinded, pre-planned interim assessment of the "effective SD" during the final month (adjusted by correlation with baseline given that they were on experimental or control therapy) after 68 women had completed the trial. (see also Amendment 6)

Amendment #2 (2.4 Protecting against bias)

When it became clear that the enrolment goal had to be changed (Amendment # 1), a further year of recruitment was allowed by the Data Safety and Monitoring Committee. However, CIHR funding was not sufficient to cover this. The PI applied to Besins Healthcare International who, through the University of British Columbia and UILO agreed to and provided $40,306.00 to fund the extension of this trial with a continued commitment to have no role in the design, conduct, analysis or publication of the study.

Amendment #3 (2.8 Primary and secondary outcome measures)

The Final Questionnaire (as in the previous progesterone for menopausal RCT[43]) included an unnamed instrument that asked several questions about overall three-month changes (decreased by up to 5 points [0 to -5] or increased by up to 5 point [0 to +5]) in VMS and in quality of sleep and characteristics of flow. This instrument is now named "Women's Perceived Changes Questionnaire" and has become a secondary outcome.

We have also included at baseline and the final visit the CeMCOR Perimenopausal Interference Questionnaire (CeMCOR PIQ) as used in the Perimenopause Experiences Project. The within-woman body and mood changes in interference with usual activities of these two likert-type measures by therapy assignment are also a secondary outcome and will further be analyzed together as a single score.

Finally, the DSMC, partially into the RCT, recommended that we add the Personal Health Questionnaire-9 (PHQ-9) to screen out potential participants who might be depressed or suicidal. We followed their instructions but also elected to include the PHQ-9 at the Final Visit and to assess within-woman changes in the PHQ-9 score as a secondary outcome.

Amendment #4 (**PRIMARY OUTCOME)**

We will also do subgroup analyses of VMS Score by Early Perimenopause (no skipped period or <60 day cycle length) and by Late Perimenopause (those with skipped or ≥60 day cycle lengths).

Amendment #5 (SECONDARY OUTCOMES)

1. Women's Perceived Changes Questionnaire of changes (from -5 to 0 to +5) in Daytime Hot Flushes and Nighttime Night Sweats and Hot Flushes (both number and severity) as recorded on the Final Questionnaire and by subgroup for Early and Late Perimenopause.
2. Women's Perceived Changes Questionnaire of changes (from -5 to 0 to +5) in the quality of sleep over the three months of the trial as assessed by the Final Questionnaire based on their random assignment to the progesterone or placebo arms of this RCT and by Early/Late

perimenopause. (This is in addition to the listed secondary outcome: "sleep problems" from the Daily Perimenopause Diary/Perimenopause Hot Flush and Night Sweat Calendar.)

3. Within-woman changes in baseline and end-of-trial perceptions of interference of perimenopausal **body changes** and **mood changes** with usual activities (as recorded by the CeMCOR Perimenopause Interference Questionnaire [CeMCOR PIQ] at baseline and final) and in the within-woman mean of the two assessments (body and mood) scored together in women randomized to the progesterone versus to placebo and by Early/Late Perimenopause.
4. Vaginal flow (see separate Flow Study protocol) related to progesterone therapy in perimenopause will be assessed based on Women's Perceived Changes Questionnaire of changes in the experience of menstrual flow/vaginal bleeding (-5/+5) from the Final Questionnaire, and/or change in their Diary/Calendar recorded use of sanitary products or volume of flow recorded by use of a menstrual cup compared with the same experiences in women randomized to placebo.
5. Depression related to progesterone therapy in perimenopause will be assessed based on the Personal Health Questionnaire-9 (PHQ-9) score changes within-woman from baseline to the end-of-trial compared with the women randomized to placebo.

Amendment #6 (2.11 Sample size)

A pre-planned evaluation of sample size was undertaken after 68 women had completed the study. This involved evaluation of the SD of the VMS Score in the final month without regard to random study group assignment. An **effective standard deviation (SD) of ~ 9** in the Vasomotor Symptom Score SD over the last 4 weeks of experimental therapy was discovered after adjustment for the fact that the final and the run-in SD values correlated with an r of 0.56. This interim assessment was blinded and without knowledge of the therapy. The original estimated SD of 6.25 was used in our application to CIHR. This re-evaluation of sample size led to an increased enrolment of goal of 245.