PROTOCOL

Title: **Treatment of Menstrual Cramps in Young Adult Women—RCT of standard versus experimental dosing of ibuprofen**

Lay Title: Ibuprofen for Menstrual Cramps

Protocol Date: November 8, 2024

Amendment 1 Date: February 14, 2025
Amendment 2 Date:
Amendment 3 Date:
Amendment 4 Date:
Amendment 5 Date:
Amendment 6 Date:

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1 BACKGROUND INFORMATION AND RATIONALE (focused literature review)

Introduction

Up to 94% of adolescent girls and young women experience menstrual cramps (cramps, also called "primary dysmenorrhea", PD), of which over 30% report moderate to severe pain and for 20-30% increased school / work absenteeism and carrying the potential risk for development of chronic pain. Current guidelines recommend Nonsteroidal Anti-inflammatory Drugs (NSAIDs) as the first line treatment, with standard cramp therapy as 400 mg ibuprofen initially, then 200 mg every 4-8 hours. However, only 45-53% of women using ibuprofen for cramps report sufficient or effective pain relief, according to a 2014 Cochrane meta-analysis. This may be explained by the current regimen failing to take into account ibuprofen's short half-life of 1.6-2 hours and its need to work "upstream" (via blocking prostaglandin synthesis). Despite our extensive clinical and instructional experience (https://www.cemcor.ca/resources/painful-periods), a more frequent dosing regimen that better aligns with drug characteristics has never previously been tested. This proposal is to test an intense (as-soon-as-cramps-start-to-return) ibuprofen dosing regimen vs a standard of care regimen for the treatment of menstrual cramps.

Relevant Literature and Data

Introduction

Primary dysmenorrhea is a term used to describe what are commonly called "menstrual cramps" that often begin in adolescence and are not attributed to any underlying pelvic pathology[1]. Multiple studies have demonstrated the impact of menstrual cramps on daily activities, attitudes toward cycles and quality of life. In an Australian population-based, cross-sectional study of 1066 adolescents aged 15 to 19 years, approximately 44.2% reported severe period pain, 35.7% reported a significant interference with daily activities and 13.7% missed school due to menstrual cramps[2]. In a cross-sectional Canadian study, it was found that among female students, 17% continued to miss classes because of menstrual cramps[3]. An earlier population-based Canadian survey in 386 teen-young women aged 14 to 21 years old found that approximately 93% reported feeling menstrual discomfort, with 70% having tried over-the-counter medications to treat this discomfort[4]. In the early 1989s, Andersch and Milsom studied a random sample of 656 aged 19-year-old women living in an urban Swedish population[5]. They documented that 72% of women reported dysmenorrhea; 15% of these women experienced limitations to their daily activities and found no improvement with analgesics. In this cohort, dysmenorrhea was significantly more severe in those experiencing an early menarche, heavier menstrual flow, in nulliparous women as well as in those who had experienced a spontaneous or medical abortion. Height, weight and regularity of menstrual cycles, however, had no significant impact on the severity of dysmenorrhea in this large late-teen Swedish population. Thus, population-based evidence shows that primary dysmenorrhea is common and is often poorly treated with current anti-inflammatory medications[2–5]. In general, menstrual cramps are underrepresented in research and may be ignored by healthcare providers (HCP) despite being the most common gynecological condition among menstruating people[1–5].

Pathogenesis of Primary Dysmenorrhea/Menstrual Cramps

Currently, overproduction of prostaglandins by the myometrium and endometrium is the pathophysiological explanation for menstrual cramps that has the most evidence[1,6]. During endometrial sloughing there are increased levels of prostaglandin F2α and prostaglandin E2. These two prostaglandins cause myometrial hypercontractility resulting in ischemia of the uterine muscle (F2α) and increased sensitivity of nociceptive nerve endings (E2) respectively[1,6].

Women and menstruating people have an increased production of prostaglandins during the documented luteal phase relative to the follicular phase of the menstrual cycle[1,7]. People with menstrual cramps tend to have higher levels of prostaglandins compared to people without menstrual cramps. These observations were confirmed through a study comparing endometrial biopsies, menstrual fluids and endometrial jet washings sampled during the luteal phase[8]. Although it is clear that uterine prostaglandins are related to menstrual cramps, the pathophysiology of the trigger to endometrial sloughing and increased prostaglandin production remains unclear.

Until recently, it has been thought that dropping progesterone levels prior to flow are the trigger for endometrial/myometrial prostaglandin production[8]. It follows from that notion that menstrual cramps only occur in ovulatory menstrual cycles. However, increasing evidence suggests that is not correct[9,10]. A prospective, 1-year observational study involving 53 women and nearly 700 menstrual cycles demonstrated that menstrual cramps likely even occur during anovulatory cycles[9]. A cross-sectional study during the SARS-CoV-2 pandemic showed more intense cramps in 35 anovulatory cycles compared with 40 normally ovulatory cycles[10]. Previous physiological research in a primate model showed that progesterone suppressed prostaglandin F2α (with or without high estradiol)[11]. Subsequently, it is necessary again to research triggers for prostaglandin release.

The Role of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) For Menstrual Cramps

The goals of treating menstrual cramps are to provide adequate pain relief so that women will be are able to participate in their usual activities. It is likely that cramp pain control will decrease absenteeism at work or school and improve overall health related quality of life[12,13]. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin production and thus decrease menstrual cramp pain[7,11,14]. Consequently, NSAIDs are considered first-line therapy in treating menstrual cramps as indicated in the guidelines recommended by the Society of Obstetricians and Gynecologists of Canada, as well as the American College of Obstetricians and Gynecologists[12,13].

NSAIDs are analgesics that inhibit cyclooxygenase (COX) which is an enzyme responsible for forming prostaglandins[15]. There are two isoforms of this enzyme: COX-1 and COX-2. COX-2 inhibition is primarily thought to relieve pain and inflammation, while the inhibition of COX-1 is related to the side effects of NSAIDs including gastrointestinal (GI) symptoms. Traditional NSAIDs, such as ibuprofen, are considered non-selective since they act on both COX-1 and COX-2 thereby leading to more adverse GI symptoms when compared to newer COX-2 selective drugs.

A study conducted by Chan et al. (1981) examined menstrual cramp intensity and prostaglandin release following prophylactic versus therapeutic treatment using 400mg of ibuprofen[16]. The severity of menstrual cramps was assessed in two ways. Firstly, a symptom chart was provided to the participants asking them to rate the cramp intensity as none, mild, moderate or severe. This chart also asked the participants to indicate whether they experienced systemic symptoms such as headaches, nausea, diarrhea, vomiting and dizziness. Secondly, menstrual fluid was collected from pre-weighed tampons and specimens were extracted to determine the amount of prostaglandins present between 16-32 hours following collection. Results showed that both the therapeutic (received ibuprofen at the onset of menses) and prophylactic groups (received ibuprofen 3 days before the next expected period) indicated good to excellent pain relief. Seven of 11 therapeutic treated people and 16 of the 20 participants treated prophylactically had adequate pain relief; both are significantly greater than placebo-treated participants[14]. There was also a significant association between pain relief and reduced menstrual prostaglandin release with ibuprofen treatment in both groups. However, there were still a substantial number of participants across both groups (20-36% of participants) who were not experiencing adequate suppression of menstrual pain at this dosing regimen[16].

Lack of consistent, effective treatment of menstrual cramps is further documented by review. In a review of 51 clinical trials conducted by Owen (1984), 18% of participants experienced minimal to no relief of menstrual cramp pain upon using NSAIDs[17]. Additionally, a systematic review conducted by Marjoribanks et al. (2015) compared all NSAID drugs used to treat primary dysmenorrhea and paracetamol as well as placebo to assess the safety and effectiveness of these therapies[18]. This review measured pain relief using dichotomous data where participants described no pain relief versus moderate pain relief for example on a visual analogue scale (VAS) of 1-10. Results showed that NSAIDs were 4.5 times more effective at relieving pain compared to a placebo, and twice as effective as acetaminophen. Analysis documented that, if 18% of women taking a placebo experienced either moderate or excellent relief of pain, then between 45% to 53% of women taking NSAIDs will also[18]. Varying NSAIDs were shown to have comparable efficacy and safety in managing menstrual cramps. However, the study showed that there were adverse GI and neurological effects such as indigestion and drowsiness associated with NSAID use.

Despite widespread NSAID availability, menstrual cramps still cause high-school adolescents in the United States to miss classes[19]. A cross-sectional study conducted in an urban center showed that 46% of participants reported missing at least one day monthly due to menstrual cramps despite nearly all participants using at least one medication. It is possible that the adolescents were using the medications at subtherapeutic doses. However, this may also suggest that there are other mechanisms to the pathophysiology of menstrual cramps that have yet to be clarified. In order to pursue treatments for women experiencing menstrual cramps that are unresponsive to NSAIDs, it is essential to elucidate these mechanisms. But first we need to review what is known about the adverse effects of the most commonly indicated NSAID for cramps, ibuprofen.

Adverse Effects of Ibuprofen

Although ibuprofen is quite effective, it is not without risks. Risks are lower with the occasional use of over the counter (OTC) NSAIDs, but the use of these products is not routinely monitored by health care providers and so users may be at risk of unrecognized adverse drug reactions[20]. Common side effects include gastrointestinal discomfort, nausea, and headaches. More serious adverse effects, though less common, can include gastrointestinal bleeding, renal impairment, and increased cardiovascular risks. Factors that increase the likelihood of adverse effects include long-term use, high doses, and pre-existing health conditions. Menstrual cramp treatment with NSAIDs typically takes place over 1-3 days and are usually at OTC doses (200-400 mg every 4-6 hours, not exceeding 1200 mg/day) which this use is less likely to cause adverse effects[27].

The meta-analysis by Marjoribanks et al. (2015) compiled 25 studies and demonstrated that the pooled results of any NSAID treatment for menstrual cramps has a 1.29 [1.11, 1.51] odds ratio for experiencing adverse effects of any kind, the most common being mild GI or neurological symptoms[18]. Ibuprofen accounted for 5% of the adverse effects across the pooled 25 studies, while the 13 other NSAIDs analyzed caused 95% of side effects. Overall, there is a lack of high-quality data accurately measuring adverse drug reactions (ADRs) specifically to ibuprofen in the management of menstrual cramps[18,21,23]. A network meta-analysis on OTC analgesics for primary dysmenorrhea postulated that this lack in data may be because the studies included were outdated and did not thoroughly describe their research methods[21]. This meta-analysis included 35 trials with a total of 4383 participants and found no significant difference in safety between naproxen, ibuprofen, diclofenac, aspirin, ketoprofen, and placebo. Diclofenac was found to be the most effective NSAID for primary dysmenorrhea, with ibuprofen coming in as a close second[21]. Despite this, that comprehensive review recommended ibuprofen as the optimal primary treatment due to its overall balance of efficacy and safety. In a cross-sectional study involving 550 female university students, the effect of mefenamic acid, ibuprofen and paracetamol were assessed from participant questionnaire results[22]. The study found no significant differences in the adverse effects reported among these medications and no single NSAID demonstrated superior effectiveness in relieving pain compared to the others. No serious ADRs were reported in any of the studies reviewed.

A recent study by Gobba et al. (2024) found that 19% of 129 female Makerere University students using ibuprofen for menstrual cramps experienced gastrointestinal (GI) adverse effects, such as nausea, ulcers, and diarrhea[23]. However, the study's descriptive nature, reliance on self-reported data, lack of dosing details, and absence of comparisons with other treatments limit its ability to accurately assess GI effects of ibuprofen. While nausea was identified as a primary adverse effect, it could also stem from pain of untreated cramps or high estrogen levels[5], and diarrhea may result from high prostaglandin levels alone[24].

Observational studies have documented a slightly increased absolute risk in cardiovascular (CV) events associated with all NSAIDs including short-term doses of ibuprofen. For example, a large study in a healthy Danish population associated an increased risk of myocardial infarction with high doses of ibuprofen (>1200mg/day) in

patients aged 30 to 50 years old, while low doses showed no such risk[25]. Importantly, however, in subgroup analyses for those aged 10 to 30, cardiovascular risk was not increased[26]. Although data on CV risks from ibuprofen use for menstrual cramps is limited, it is likely negligible given the young age of our study demographic and that other risk factors such as advanced age, dyslipidemia or hypertension play a larger role[27].

Comments

The literature consistently supports the effectiveness of ibuprofen in providing pain relief for women (people with ovaries of reproductive age, PORA) who have menstrual cramps using a typical dosage of 200-400 mg every 4-6 hours, not exceeding 1200 mg/day[28]. Compared to this OTC dose, the prescription dose is 400-600 mg every 6 hours, not exceeding 2400 mg/day. However, this higher dose is typically reserved for more severe pain due to the increased risk of adverse effects.

The analgesic effects of ibuprofen begin within 30-60 minutes, reaching a maximum effect after 2 hours. It is hypothesized that more frequent dosing (200 mg every 2 hours) or repeat dosing as cramps return could prevent prostaglandin build-up and reduce the pain of cramps more effectively. Although this more frequent dosing may mean a higher than 1200 mg/24-hour dose, it is unlikely that women would need treatment for longer than three days in a single period. In this approach, participants who have a history of severe kidney disease/kidney failure or other contraindications to ibuprofen therapy will be excluded. Ultimately, a more frequent dosing regimen might allow for effective treatment with potentially mild adverse effects. While monitoring adverse effects, we can determine whether the frequent or standard dosing has more adverse effects.

Some research has observed a placebo effect in menstrual cramp treatment trials[29]. However, in the double-blinded study with 55 participants experiencing primary dysmenorrhea, the placebo effect diminished quickly over time[29]. Ideally, treatment for menstrual cramps should be guided by double-blinded trials where the administration and tracking of the treatment are conducted over multiple cycles. However, as a proof-of-concept trial, a two-week period of record-keeping starting about a week before anticipated flow should give a good indication of the effectiveness of more frequent ibuprofen dosing for menstrual cramp intensity, days of cramps and Cramps Score (intensity X duration) all versus standard dosing. We will also know, from this short study in more women (ideally 100), if adverse effects are more common.

2 STUDY OBJECTIVES

Our **research question** is: Will women perceive, compared to their last 3-months' experience, that intense ibuprofen dosing significantly decreases menstrual cramp intensity during 1-week of documented therapy compared with standard-of-care ibuprofen dosing as reported in the Final Questionnaire?

We **hypothesize** that the intense ibuprofen dosing (experimental arm) will decrease cramp intensity by 60% (Final Questionnaire recording of -3, on a -5, 0, +5 scale) compared with

recalled experiences in the last three cycles. This is based on Dr. Prior's 45-year clinical experience. She reports that 95% who have tried her recommendation report total resolution of their "cramps problem." Only those who wake with cramps are not completely free of severe cramps. We hypothesize that those in the standard-of- care ibuprofen dosing arm will have a 20% decrease (a recording of -1 on the Final Questionnaire). Why not "no change" or 0? Because control arm trial participants, who need to record the dose timing are likely to pay more attention and actually take the ibuprofen 4 hours after the last dose.

The **purpose** of this study is to determine the effectiveness and safety of intense ibuprofen dosing in PD compared to the standard of care Q 4-6-hour ibuprofen dosing.

Primary outcome measure

1. Perceived change in menstrual cramp intensity (scored -5, 0, +5) during this study compared with a person's experience in the last three months will be compared between those randomized to intensive (experimental) versus standard (control) ibuprofen dosing as recorded in the Final Questionnaire.

Secondary objectives: comparing intense (experimental) versus standard-of-care (control) groups

1. Variables relevant to participants' cramp experience: changes in feeling of self-worth, feeling of energy and outside stresses recorded before and during flow, as scored on a scale from 1-5, as recorded by daily Menstrual Cycle Diary© (Daily Diary).
2. Amount of flow as recorded by number of soaked tampons +/- pads (normal size-soaked/day); or by volume scoring if they are using a menstrual cup.
3. Gastrointestinal ibuprofen adverse effects: heartburn, stomach pain, nausea, vomiting as recorded on the Ibuprofen Therapy Recording form.
4. General menstrual flow or cramps adverse effects: headache, tiredness, diarrhea, sleep problems (on the Daily Diary and the Ibuprofen Therapy Recording form)
5. Total mgs. of ibuprofen/day taken for menstrual cramps over each of 1st to 7th menstrual cycle-days.
6. Remaining ibuprofen pill counts by random assignment.
7. Mean menstrual cramp intensity scored on a scale from 0-4, by the Daily Diary
8. Mean menstrual cramp duration as recorded >0 in the Daily Diary
9. Cramps Score = (total days with cramps X mean cramp intensity), by prospective daily Menstrual Cycle Diary© records.
10. Perceived change in the duration of cramps on the Final Questionnaire.
11. Perceived change in the impact of cramps on daily life as reported on the Final Questionnaire.

METHODOLOGY

Study Design:

This study will be a Parallel Group Randomized Controlled Trial (RCT). Eligible participants will be randomly assigned in a 1:1 ratio to one of two groups: standard ibuprofen dosing (control group) or the intense ibuprofen dosing (experimental group). Block randomization will

be used to ensure equal allocation across the groups. The prescription on the provided bottle of ibuprofen will differ between groups. To reduce predictability, prevent selection bias, and enhance robustness, different block sizes of 4 and 6 will be used. There will be no other blinding except we will ask that participants not talk with other participants about their cramp therapy. The statistician, who provides the randomization code to the pharmacy and analyzes the data will have no contact with participants and will remain blind to study arm.

Sample Size:

Sample size calculation uses proportions and extensive clinical experience in forming the estimates based on the outcome variable of "**Change in the Intensity of Cramps".** This metric is obtained in the Final Questionnaire.

It will measure on a scale of -5(decrease) to +5 (increase), where each segment contributes 20%, for example, 0 to -1 = 20% decreased.

Based on the **assumption** that the standard-of-care dose (control) group will experience a 20% reduction in cramp intensity compared to their last three month's experiences because the trial will improve their attention to pill-taking, and the intense dose (experimental) group will experience a 60% reduction in pain intensity compared to their previous experiences.

- Controls we expect a 20% decrease in cramp intensity (P1=.20) (equivalent to -1 on the Final Questionnaire)
- Experimental we expect a 60% cramp intensity reduction (P2=.60) (equivalent to -3 on the Final Questionnaire)
- Power: 90% (0.90)
- Alpha: 5% (0.05)

$n = [(Z_{\alpha/2}+Z_{\beta})^2 \times \{P1(1-P1) + P2(1-P2)\}] / (P2-P1)^2$

Where:

- $Z_{\alpha/2}$ is the critical value for a 5% significance level (two-tailed), which is 1.96.
- Z_{β} is the critical value for 90% power, which is 1.28.
- P1 and P2 are the proportions under the null and alternative hypotheses.

After accounting for an expected 20% incompletion/dropout rate, the required sample size for this RCT would be **33 participants per group** and, the total sample size for the study would be **66 participants**.

3 INVESTIGATION PLAN

Investigator's experiences

Our team includes representation from multiple disciplines. The PI (JCP) is an endocrinologist clinician-scientist with extensive research, public health and population-based study (epidemiology, CaMos) experience. The study lead (SQ) is a medical student and practicing PharmD. A second study lead is GM, a medical student with research

experience in ovulation and cramps, has initiated the literature review, while the third lead, MG, has reviewed ibuprofen adverse effects and completed the background. Other study leads are JY, also a pharmacist, who has facilitated Pure Pharmacy's engagement, and KF who has reproductive care-delivery experience during SARS-CoV-2. SS is an international medical graduate, (trained in Ob/Gyn) with an MHSc who will manage the database, randomization to the two arms and will perform all statistical analyses. AG is an international medical graduate, woman's reproductive public health expert responsible for the original planning for this study, who has now achieved Canadian Family Practice certification. DK, a basic scientist, will manage study administration and assist with recruitment. Key to making this study possible is JY, pharmacist and current medical student who formerly worked with Pure Integrative Pharmacies, and who has engaged their assistance including free provision of pharmaceutical services and all ibuprofen as well as providing courier service. We have also engaged the practicing endocrinologist (MD) to prescribe ibuprofen (thus allowing the potential for dispensed, rather than over-the-counter, drug dosing), and a community pharmacist working with Pure Integrative Pharmacies who will be making the ibuprofen bottles available for study dispensing.

Duration of Study Participation

The study duration per participant will be up to 16 days, with one day of screening and enrolment, 7 premenstrual days and 7 flow and follicular phase menstrual cycle-days for independent data collection, and 1-2 days for follow-up (submitting Daily Diary©, Ibuprofen Therapy Recording form, and completing a Final Questionnaire, plus providing unused pills that will quickly be counted and returned to the volunteer).

Study Population

Inclusion Criteria—resident within Metro Vancouver with access to our offices in the Diamond Centre near Vancouver General Hospital

1. Menstruating individuals 16-25 years of age
2. Regular menstrual cycles, approximately one-month apart (range 21-35 days or 3-5 weeks)
3. Moderate to severe menstrual cramps (problematic cramps) interfering with daily life and activities (as defined by the screening questionnaire)
4. If sexually active with a man, may be using non-hormonal contraceptives (condoms, diaphragm either or both with vaginal spermicide, or the copper IUD)

Exclusion Criteria

1. Hormonal contraceptive use (including combined hormonal contraceptives, levonorgestrel -releasing IUDs*, hormonal implant, Depo-Provera, progestin-only pill) and emergency contraceptives within the last cycle, or any reproductive hormone use within last 3 months.
2. Have inability to take or should not take ibuprofen as described by the screening questionnaire. For example, a hypersensitivity to ibuprofen or other NSAIDs or any ingredients in the formulation of the ibuprofen tablets, which may include microcrystalline cellulose, croscarmellose sodium, magnesium stearate, colloidal

silicon dioxide, hydroxypropyl cellulose, polyethylene glycol, titanium dioxide, D&C yellow #10 and FD&C yellow #6, carnauba wax.

3. Have complete or partial syndrome of acetylsalicylic acid (ASA) intolerance (rhinosinusitis, urticaria/angioedema, nasal polyps, asthma) in whom asthma, anaphylaxis, urticaria/angioedema, rhinitis or other allergic manifestations are precipitated by ASA or other NSAIDs, as per the contraindications section in the manufacturer product monograph.
4. Active gastric or duodenal ulcer, a history of recurrent ulceration, gastrointestinal bleeding, or active inflammatory disease of the gastrointestinal system. Patients with gastroesophageal reflux disease (GERD) are not excluded by these criteria.
5. Significant hepatic impairment or active liver disease.
6. History of severe kidney disease defined as eGFR <30ml/min.
7. Have suffered from an acute kidney injury (serum creatinine rise of 26 μM) in the past 6 weeks due to significant fluid loss.
8. Have systemic lupus erythematosus, as anaphylaxis-type reactions with fever have been documented to occur when ibuprofen has been administered previously, as per the contraindication's sections in the manufacturer product monograph.
9. Endometriosis (by history, imaging or surgery).
10. Pregnant or post-partum for less than 6 weeks.

*****_Note: If we run into difficulty recruiting enough participants, we will consider including individuals with regular cycles (i.e., approximately a month apart) over the last 3 months, who have worn Kyleena for 60 days or Mirena for 5 years._

Study Procedures

Once volunteers sign-up for the study, they will be contacted via phone or text to determine eligibility using the inclusion and exclusion criteria as mentioned above. After participants are enrolled, they will be invited to attend two visits: the first to take place before starting the study (for orientation and counselling), and the second after they have had the 7 days in the next cycle when they have used ibuprofen for cramps. At the study end, we will ask them to do one further questionnaire, count their remaining ibuprofen pills, and offer them a free Diva® Menstrual Cup if they wish, after providing both verbal and written use instructions.

At the orientation visit, participants will be asked to sign an informed consent form and go through the baseline questionnaire, including weight and height measurements. They will receive general medication counselling on ibuprofen as a prescription (*e.g.,* maximum dose = 12 tablets of ibuprofen [200 mg] every 24 hours) and on potential adverse effects to monitor for. They will also be oriented on how to fill out the Cramps Diary form, including how to record the time they take ibuprofen and any adverse events they experience (with abbreviated letters). We will also provide standardized teaching on how to count the number of tampons/pads soaked per day.

4 STUDY EVALUATION AND MEASUREMENTS

Screening and Monitoring Evaluations and Measurements

Recruitment

This will be a randomized, one-week, open-label (all participants will know they are taking ibuprofen) but semi-blinded (the 2 groups will have different prescribed regimens), comparative, 2-arm interventional study. We will enroll 66 eligible menstruating individuals from Metro Vancouver utilizing CeMCOR's website, social media and community outreach via engagement of local partners (McCreary Centre, Options for Sexual Health, Vancouver Women's Health Collective, YWCA) as well as high schools and post-secondary institutions. Consent forms will be sent to all inquirers, and upon verbal agreement, participants will be screened by telephone or video conferencing to confirm eligibility.

Randomization and Screening

Randomization will be by performed by SS (who will not have direct participant contact) using a computer random number generator to select random permutated blocks into an equal allocation ratio. Once eligible and randomized into the control vs experimental arms, they will be interviewed via video-conferencing with a relevant portion of the Youth CaMos Questionnaire. This will include variables such ethnicity, family menstrual cramps history, age at menarche, pregnancy, contraception, lifestyle including exercise, cigarette/vape and alcohol use. Participants will be asked to not talk with others who might be in the study.

Monitoring and Recording

Instructions on how to keep the Daily Diary (**Figure 1**) will be provided to the participants over phone/video conferencing plus access to a video https://www.youtube com/watch?v=6K9LB6afKxE. They will be taught to score cramps as 1- mild, 2- moderate, 3- moderately intense and 4- very intense. We will also train all to use the Ibuprofen Therapy Recording form (**Figure 2**) for recording the time and dose of ibuprofen taken on each of the days. We will also instruct them to circle the letter of the alphabet (at the bottom of the form) to record any adverse effects, *e.g.,* "H" = headache. At the end of the study, all will complete the Perceived Cramp Change instrument (**Final Questionnaire**).

Intervention

Prescriptions of 90 **ibuprofen** 200 mg tablets will be dispensed to all participants from a standard lot (Apotex Canada, Lot #____, exp ____).

All participants will be advised to take 2 tablets (= 400mg) with food/milk ***at the first hint*** of cramps.

Experimental (***intense*** ibuprofen dosing): Their prescription will read "Following the initial 400 mg dose with food/milk, take another 200 mg tablet with food/milk as soon as

cramps start to return, even if this is only 1-2 hours since the last dose, to a maximum of 12 tabs every 24 hours."

Control (standard-of-care ibuprofen dosing): Their prescription will read, "Following the initial 400 mg dose with food/milk, take another 200 mg tablet with food/milk every 4-6 hours for ongoing menstrual cramps, to a maximum of 12 tabs every 24 hours."

Efficacy Evaluations (NA)

Safety Evaluation

Participant safety will be monitored by adverse events, including gastrointestinal ibuprofen adverse effects (*e.g.*, heartburn or acid/stomach pain, nausea, vomiting) and general menstrual flow "period"/cramps adverse effects (*e.g.,* headache, tiredness, diarrhea, sleep problems) reported at the time of taking each tablet on the Ibuprofen Therapy Recording form with some experiences that are duplicated on the Daily Diary©.

5 STATISTICAL CONSIDERATIONS

Statistical Methods

We will assess all variables for their distribution, using parametric statistics for analysis if normally distributed, and for those from the Daily Diary, that are an ordinal scale, will use non-parametric methods.

Baseline characteristics of those enrolled in each of the two groups will be compared to ensure appropriate randomization (age, ethnicity, height, weight, age at menarche and other variables found relevant to cramps experience in the whole cohort. Baseline and demographic characteristics will be summarized by standard descriptive summaries (*e.g.,* means and 95% CI for continuous variables such as age and percentages for categorical variables such as cigarette use).

We currently have no data with which to perform a power calculation. Therefore, we will use the Final Questionnaire on Perceived Change in cramp intensity and an estimated percentage decrease of 60% (or a recording of -3 on a -5 to 0 to +5 change scale) in menstrual cramps on intense ibuprofen dosing based on Dr. Prior's extensive clinical experience. We will also estimate that those on standard-of-care ibuprofen dosing (Q4-6 hours) will record -1 (a decrease of 20%) on the Final Questionnaire based on paying attention and taking ibuprofen at 4-hourly intervals. We further estimate that 20% of those who are eligible and enroll will not complete the whole trial and Final Questionnaire.

Analysis of Primary Objective

The primary analysis will include all participants who have met inclusion and exclusion criteria, and agreed to be in the study. Some may drop out; we can only analyze data for those who have completed the trial.

Primary objective: Perceived change in menstrual cramp intensity (scored -5, 0, +5) during this study compared with a person's experience in the last three months will be

compared between those randomized to intensive (experimental) versus standard (control) ibuprofen dosing as recorded in the Final Questionnaire.

Secondary objective (see above, page 7)

6 SAFETY MANAGEMENT (N/A)

We will ask all participants that, if they have severe vomiting or any blood in their vomit, they immediately stop taking ibuprofen and see their family doctor or go to emergency.

7 STUDY ADMINISTRATION

Data Collection and Management

We will be keeping a master list containing personal information (address, contact data) and ID numbers separate from data documents that only contain ID number. Both will be stored as password-protected files restricted to authorized investigators only. For security and data backup purposes, a copy of the file will be saved on the CeMCOR's K drive (server backed every 5 minutes by MedIT), with the original in a locked cabinet in a locked research room in the Diamond Centre. Any participant identifiers that can be linked to personal information will be destroyed after research results publication.

Data sources (if applicable, for existing records)

N/A

Confidentiality

All data and records generated in this study will be kept confidential and will not be used for any purpose other than conducting the study. Each participant will be assigned a unique ID number, and identifying data (any identifying or corresponding personal information) will be locked in a password-protected file.

Regulatory and Ethical Considerations

All participants will sign informed consent to a UBC Clinical Research Ethics Board approved protocol. Those participants younger than age 19 will be counselled by a physician to ensure they are able to understand the study, its risks and procedures and to provide informed consent. The study as an RCT will require trial registration which we are currently completing through ISRCTN. However, it will not require Health Canada CTA because ibuprofen is the standard and usual therapy for menstrual cramps (PD).

8 PUBLICATION

Journals of interest:

1. *Canadian Medical Association Journal*
2. *Human Reproduction*
3. *The Journal of Clinical Endocrinology & Metabolism*

4. *PLOS Medicine*
5. *Perspective on Sexual and Reproductive Health*
6. *PLOS ONE*
7. *Journal of Midwifery and Women's Health*
8. *Women's Health (SAGE)*
9. *Women's Reproductive Health*

9 REFERENCES

1. Iacovides S, Avidon I, Baker FC. What we know about primary dysmenorrhea today: A critical review. Hum Reprod Update. 2015;21(6). doi:10.1093/humupd/dmv039

2. Parker MA, Kent AL, Sneddon A, Wang J, Shadbolt B. The Menstrual Disorder of Teenagers (MDOT) Study No. 2: Period ImPact and Pain Assessment (PIPPA) Tool Validation in a Large Population-Based Cross-Sectional Study of Australian Teenagers. J Pediatr Adolesc Gynecol. 2022;35(1). doi:10.1016/j.jpag.2021.06.003

3. Burnett, M., Antao, V., Black, A., Feldman, K., Grenville, A., Lea, R., Lefebvre, G., Pinsonneault, O., Robert, M. (2005). Prevalence of Primary Dysmenorrhea in Canada. Journal of obstetrics and gynaecology Canada, 27(8), 765-770. http://dx.doi.org/10.1016/S1701-2163(16)30728-9

4. Campbell MA, McGrath PJ. Use of medication by adolescents for the management of menstrual discomfort. Arch Pediatr Adolesc Med. 1997;151(9). doi:10.1001/archpedi.1997.02170460043007

5. Andersch B, Milsom I. An epidemiological study of young women with dysmenorrhea. Am J Obstet Gynecol. 1982;144:655-660.

6. Dawood MY. Dysmenorrhoea and Prostaglandins: Pharmacological and Therapeutic Considerations. Drugs. 1981;22(1). doi:10.2165/00003495-198122010-00003

7. Pickles VR. PROSTAGLANDINS AND DYSMENORRHEA: Historical Survey. Acta Obstet Gynecol Scand. 1979;58(87 S). doi:10.3109/00016347909157782

8. Dawood MY. Primary dysmenorrhea: Advances in pathogenesis and management. Obstetrics and Gynecology. 2006;108(2). doi:10.1097/01.AOG.0000230214.26638.0c

9. Bann, S., Goshtasebi, A., Shirin, S., & Prior, J. C. (2022). A one-year observational cohort study of menstrual cramps and ovulation in healthy, normally ovulating women. *Scientific reports*, *12*(1), 4738. https://doi.org/10.1038/s41598-022-08658-3

10. Mann, G., Shirin, S., Bann, S., Yong, P. J., Kalidasan, D., Goshtasebi, A., & Prior, J. C. (2024). Menstrual Cramps in Anovulatory versus Normally Ovulatory Cycles - SARS-COV-2 Pandemic Daily Data Plus a Meta-Analysis of Cramps and Anovulation. *Journal of pain research*, *17*, 2363–2374. https://doi.org/10.2147/JPR.S457484

11. Eldering, J. A., Nay, M. G., Hoberg, L. M., Longcope, C., & McCracken, J. A. (1990). Hormonal regulation of prostaglandin production by rhesus monkey endometrium. *The Journal of clinical endocrinology and metabolism*, *71*(3), 596–604. https://doi.org/10.1210/jcem-71-3-596

12. ACOG Committee Opinion No. 760: Dysmenorrhea and Endometriosis in the Adolescent. Obstetrics and Gynecology. 2018;132(6). doi:10.1097/AOG.0000000000002978

13. Burnett M, Lemyre M. No. 345-Primary Dysmenorrhea Consensus Guideline. Journal of Obstetrics and Gynaecology Canada. 2017;39(7). doi:10.1016/j.jogc.2016.12.023

14. Funk CD. Prostaglandins and leukotrienes: Advances in eicosanoid biology. Science (1979). 2001;294(5548). doi:10.1126/science.294.5548.1871

15. Shi S, Klotz U. Clinical use and pharmacological properties of selective COX-2 inhibitors. Eur J Clin Pharmacol. 2008;64(3). doi:10.1007/s00228-007-0400-7

16. Chan WY, Yusoff Dawood M, Fuchs F. Prostaglandins in primary dysmenorrhea. Comparison of prophylactic and nonprophylactic treatment with ibuprofen and use of oral contraceptives. Am J Med. 1981;70(3). doi:10.1016/0002-9343(81)90576-3

17. Owen PR. Prostaglandin synthetase inhibitors in the treatment of primary dysmenorrhea: Outcome trials reviewed. Am J Obstet Gynecol. 1984;148(1). doi:10.1016/S0002-9378(84)80039-3

18. Marjoribanks J, Ayeleke RO, Farquhar C, Proctor M. Nonsteroidal anti-inflammatory drugs for dysmenorrhoea. Cochrane Database of Systematic Reviews. 2015;2015(7). doi:10.1002/14651858.CD001751.pub3

19. O'Connell K, Davis AR, Westhoff C. Self-treatment Patterns among Adolescent Girls with Dysmenorrhea. J Pediatr Adolesc Gynecol. 2006;19(4). doi:10.1016/j.jpag.2006.05.004

20. Moore, N., Pollack, C., & Butkerait, P. (2015). Adverse drug reactions and drug-drug interactions with over-the-counter NSAIDs. *Therapeutics and clinical risk management*, *11*, 1061–1075. https://doi.org/10.2147/TCRM.S79135

21. Nie, W., Xu, P., Hao, C., Chen, Y., Yin, Y., & Wang, L. (2020). Efficacy and safety of over-the-counter analgesics for primary dysmenorrhea: A network meta-analysis. *Medicine*, *99*(19), e19881. https://doi.org/10.1097/MD.0000000000019881

22. Karout, S., Soubra, L., Rahme, D., Karout, L., Khojah, H. M. J., & Itani, R. (2021). Prevalence, risk factors, and management practices of primary dysmenorrhea among young females. *BMC women's health*, *21*(1), 392. https://doi.org/10.1186/s12905-021-01532-w

23. Gobba, S., Kibone, W., & Kiguba, R. (2024). Self-reported gastrointestinal adverse effects of non-steroidal anti-inflammatory drugs in female students with dysmenorrhoea at Makerere

University: prevalence, discontinuation and associated factors. a cross sectional study. *BMJ open*, *14*(6), e079660 https://doi.org/10.1136/bmjopen-2023-079660

24. Hawkey, C.J., Rampton, D.S. (1985). Prostaglandins and the gastrointestinal mucosa: Are they important in its function, disease, or treatment? Gastroenterology, 89(5), 1162-88. https://doi.org/10.1016/0016-5085(85)90225-2

25. Fosbøl EL, Gislason GH, Jacobsen S, et al. (2009). Risk of myocardial infarction and death associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) among healthy individuals: a nationwide cohort study. *Clin Pharmacol Ther.* **85**(2):190–197

26. Schjerning, A. M., McGettigan, P., & Gislason, G. (2020). Cardiovascular effects and safety of (non-aspirin) NSAIDs. *Nature reviews. Cardiology*, *17*(9), 574–584. https://doi.org/10.1038/s41569-020-0366-z

27. Moore N, Salvo F, Duong M, Blin P, Pariente A. (2014). Cardiovascular risks associated with low-dose ibuprofen and diclofenac as used OTC. *Expert Opin Drug Saf.* **13**(2):167–179.

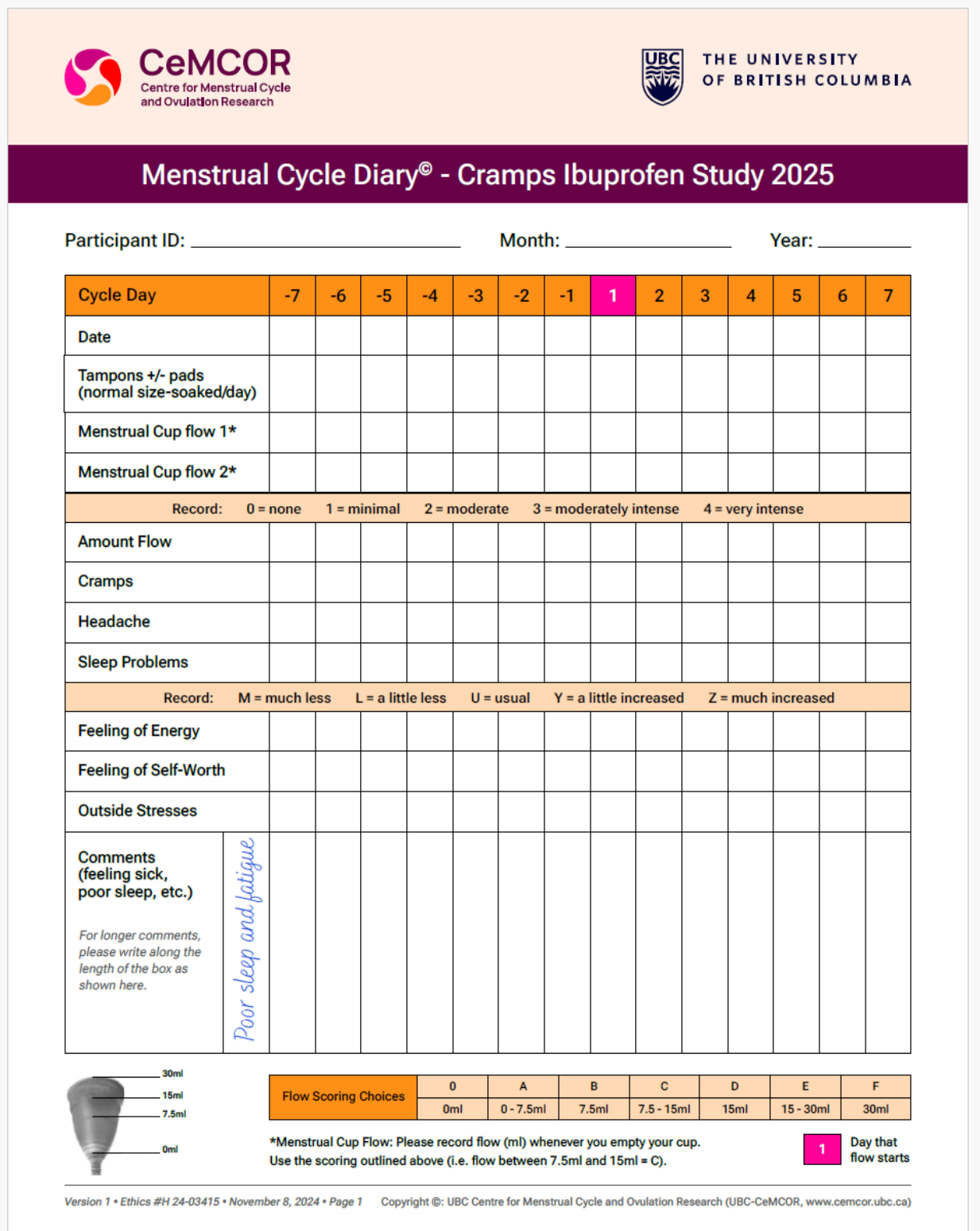
28. Hersh, E. V., Moore, P. A., & Ross, G. L. (2000). Over-the-counter analgesics and antipyretics: a critical assessment. *Clinical therapeutics*, *22*(5), 500–548. https://doi.org/10.1016/S0149-2918(00)80043-0

29. Fedele, L., Marchini, M., Acaia, B., Garagiola, U., & Tiengo, M. (1989). Dynamics and significance of placebo response in primary dysmenorrhea. *Pain*, *36*(1), 43–47. https://doi.org/10.1016/0304-3959(89)90110-3

APPENDIX

Truncated 14-day Menstrual Cycle Diary© (**Figure 1**)
Ibuprofen Therapy Form & Adverse Effects (**Figure 2**)
Perceived Cramps Change (**Final Questionnaire**)

Figure 1



CeMCOR
Centre for Menstrual Cycle and Ovulation Research

THE UNIVERSITY OF BRITISH COLUMBIA

Menstrual Cycle Diary© - Cramps Ibuprofen Study 2025

Participant ID: _____ Month: _____ Year: _____

Cycle Day	-7	-6	-5	-4	-3	-2	-1	1	2	3	4	5	6	7
Date														
Tampons +/- pads (normal size-soaked/day)														
Menstrual Cup flow 1*														
Menstrual Cup flow 2*														
Record: 0 = none 1 = minimal 2 = moderate 3 = moderately intense 4 = very intense														
Amount Flow														
Cramps														
Headache														
Sleep Problems														
Record: M = much less L = a little less U = usual Y = a little increased Z = much increased														
Feeling of Energy														
Feeling of Self-Worth														
Outside Stresses														
Comments (feeling sick, poor sleep, etc.) *For longer comments, please write along the length of the box as shown here.*	*Poor sleep and fatigue*													

30ml
15ml
7.5ml
0ml

Flow Scoring Choices	0	A	B	C	D	E	F
	0ml	0 - 7.5ml	7.5ml	7.5 - 15ml	15ml	15 - 30ml	30ml

*Menstrual Cup Flow: Please record flow (ml) whenever you empty your cup. Use the scoring outlined above (i.e. flow between 7.5ml and 15ml = C).

1 Day that flow starts

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Figure 2

CeMCOR Centre for Menstrual Cycle and Ovulation Research

THE UNIVERSITY OF BRITISH COLUMBIA

Ibuprofen Therapy Recording Form for Problematic Menstrual Cramps

Please record the time you took two ibuprofen pills at the start of cramps. All other times are for the next 200 mg tablet you take. Please put a star (*) on the Study Day your period started.

Participant ID:______________ Ibuprofen Start Date:__________

*Unwanted Effects: Please CIRCLE the initials of what you experienced	0 = None; A = Acid/Stomach Pain; N = Nausea; V = Vomiting; H = Headache; D = Diarrhea; T = Tired or low energy

Study Day	1	2	3	4	5	6	7	8	9
Time taken									
Unwanted Effects*	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T
Time taken									
Unwanted Effects*	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T
Time taken									
Unwanted Effects*	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T
Time taken									
Unwanted Effects*	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T
Time taken									
Unwanted Effects*	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T
Time taken									
Unwanted Effects*	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T
Time taken									
Unwanted Effects*	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T
Time taken									
Unwanted Effects*	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T	0 A N V H D T

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Final Questionnaire

The University of British Columbia

Treatment of Menstrual Cramps in Young Adult Women— RCT of standard versus experimental dosing of ibuprofen

Study ID #: Date:

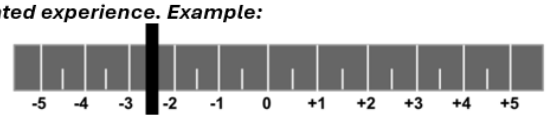
Centre for Menstrual Cycle & Ovulation Research
Division of Endocrinology, Department of Medicine
Gordon and Leslie Diamond Health Care Centre
2775 Laurel Street/ Rm 4111, Vancouver, V5Z 1M9
cycles.cemcor@ubc.ca

Standard vs Intense Ibuprofen Dosing – Final Questionnaire

Thank you for participating in our study.

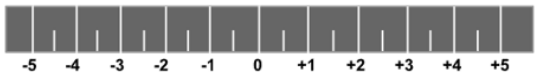
To better understand the **changes** in cramps you've experienced during this study, please answer the following questions based on your observations of your most recent cycle compared with the last **three** menstrual cycles. *If you draw a line to the right of 0, they got worse; to the left means they got better.*

Please draw a vertical line through the box in a place that best reflects the* change *in your cramp-related experience. Example:



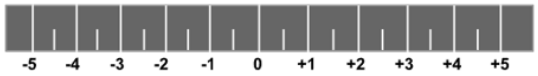
1. Intensity of Cramps

How has the intensity of your menstrual cramps during this trial CHANGED compared to the intensity of cramps you've experienced in the past three cycles?

Decreased Intensity  Increased Intensity

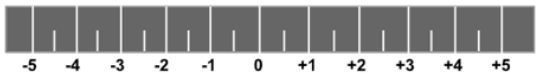
2. Duration of Cramps

How has the duration of your menstrual cramps (number of days) CHANGED during this trial compared to the duration of cramps in cycles in the past three cycles?

Decreased Duration (days)  Increased Duration (days)

3. Impact on Daily Life

How have the impact of menstrual cramps on your daily life CHANGED during this trial, compared to the cramps you experienced in the past three cycles?

Decreased Impact  Increased Impact

Use of Additional Methods for Cramp Relief During the Study

4. Did you use any additional methods to help with your cramps during the study?
   - ☐ Yes
   - ☐ No (Please go to 5)

   4.1 If yes, which methods did you use? *(Select all that apply)*
   - ☐ Exercise
   - ☐ Heating pad
   - ☐ Other (please specify) _____

5. Did you take any other medications or supplements for your cramps during the study?
   - ☐ Yes
   - ☐ No

   5.1 If yes, please provide the following details
   - Name of the medication or supplement _____
   - Dose _____
   - Frequency of use (e.g., once a day, twice a week) _____