

Study Title: Reduction of premature discontinuation of contraceptive implants by advance provision of an OCP-based participant intervention: randomized clinical trial

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Investigator Studies Program (MISP) Protocol Template

Requirements for Submitting a Full Proposal

Section #1 - MISP Protocol Identification

Study Title:	Reduction of premature discontinuation of contraceptive implants by advance provision of an OCP-based participant intervention: randomized clinical trial
Request Date:	
Institution Name	University of Colorado School of Medicine
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Funding	Investigator initiated funded by Merck

Section #2- Core Protocol

2.1 Objectives & Hypotheses

Objective:

To compare rates of etonogestrel implant discontinuation in implant initiators who are given advance provision of combined oral contraceptive pills (COCs) and a bleeding rescue regimen (COCR intervention) to participants given standard counseling (comparator).

Secondary Objectives:

1. To determine if participants initiating the contraceptive implant who are also provided COCR are more likely than participants receiving standard counseling to:
 - a. report higher levels of satisfaction with their contraceptive implant at one year following initiation
 - b. require less clinical follow-up and clinical resources in the year following initiation.
2. To determine if people who did not enroll in this randomized controlled trial are similar in characteristics and outcomes to the enrolled group and specifically compared to the “usual care” arm.

Primary Hypothesis: We hypothesize that participants who initiate the contraceptive implant and are given advance provision of COCR will be significantly less likely to discontinue their implant in the year following insertion than those given standard counseling

Secondary Hypothesis: We hypothesize that participants who initiate the contraceptive implant and receive the COCR intervention will:

- a. be more satisfied with their contraceptive implant
- b. make and attend fewer follow-up visits in the year after initiation.

2.2 Background & Rationale, Significance of Selected Topic & Preliminary Data

The contraceptive implant is a highly effective and safe contraceptive method for adolescents. Although usually well tolerated, the most common reason for early discontinuation is bleeding. The contraceptive choice study looked at LARC continuation in adolescents (under 20yo) and found that 80% of adolescent continued at 1 year and 50.8% of adolescents continued the implant at 3 years. Despite this, adolescents who do discontinue often report bleeding as the reason (Cohen 2019). Those who get the implant removed often switch to a less effective method.

Studies of interventions for bleeding in implant users have been small, brief and have rarely evaluated long term bleeding outcomes, long term continuation or satisfaction.

In a 2015 study by Guiahi et al, 32 women with self-reported bothersome bleeding and current bleeding episode of at least 7 consecutive days were randomized to COC or placebo for 14 days. They found an increased likelihood of cessation of bleeding with COCs but bleeding often resumed within a week of discontinuation. They did not look at participant satisfaction or continuation of their method. Hou et al (2016) also conducted a randomized placebo-controlled trial of bleeding with 26 participants. Most women in both arms reported bleeding improvement at 4 weeks, although those on COCs were significantly more likely to improve. They followed participants for 2 months after a 4-week treatment trial. Of 13 COC users, 8 opted to continue study treatment after the 4 weeks. Four of the 26 participants requested implant removal by 3 months. 3 of these women had used COCs at some time during the study.

	<p>Chen et al (2018) studied concurrent use of implant and COC in a proof of concept study. Two of 19 participants had the implant removed at 6 month follow up but neither requested removal for bleeding complaints. There were no adverse events and use of COCs and implant was well tolerated.</p> <p>These studies have identified that COCs may be an effective intervention for reported bothersome bleeding during implant use and are safe to use in conjunction with the implant. Whether offering a COC intervention increases satisfaction or continuation of the implant remains unexplored.</p> <p>Studies evaluating other interventions for breakthrough bleeding on the contraceptive implant have had mixed results. Mifepristone, a selective progesterone receptor modulator, is reported to up regulate endometrial estrogen receptors to induce proliferation and reduce vaginal bleeding. A study on the levonorgestrel implant (Cheng 2000) showed some improvement in episodes of unscheduled bleeding but a pilot study in etonogestrel implant users did not show clinical benefit (Weisberg 2006)</p> <p>Nonsteroidal anti-inflammatory drugs (NSAIDs) have been used to treat irregular bleeding and showed some decrease in bleeding episodes when taking three times a day for 5 days (Phaliwong P, 2004). Appropriate medication, dose and regimen have not been established.</p> <p>Other treatments including mifepristone plus estrogen or doxycycline (Weisberg E 2006), tamoxifen (Simmons 2017) and ulipristal acetate (Zigler 2018) have all been shown to have some benefit. Challenges have been found with all studies in improving bleeding patterns long term after intervention has been discontinued.</p> <p>COC's have been recommended in expert opinion as a first-choice medication to control persistent bleeding due to low cost and the most supporting evidence for short term benefit (Mansour 2011).</p> <p>Hou, et al reported that women who initially requested removal of the implant were more likely to continue to desire removal at study conclusion. It is possible that by the time participants have come to clinic for bothersome bleeding they are less willing to try an intervention or be satisfied with its outcomes. If an intervention for bleeding was provided at implant insertion to be used as needed, this could give a participant a plan for addressing this possible side effect and a sense of control over their bleeding patterns.</p>
2.3 Study Design	<p>This is a randomized controlled open-label clinical intervention trial. Participants will be recruited from the Children's Hospital Colorado BC4U clinic. This clinic is a Title X supported family planning clinic that offers free, confidential, same-day contraception to patients aged younger than 25 years. Participants will be eligible if they are 14-23.9 years old and are new starters of the etonogestrel implant. Exclusion criteria will be any contraindications to estrogen-containing birth control, and plans to move from the area (where it would not be reasonable to come to the clinic) in the next 12 months. All patients seeking contraception in our clinic undergo thorough evaluation (personal and familial health history) for contraindications to any forms of contraception that are offered as part of the contraceptive assessment and counseling process. For participants under 18 years of age, we will obtain a waiver of parental consent from the IRB. This is available because reproductive services</p>

	<p>are confidential for all adolescents in the state of Colorado, and the University of Colorado IRB recognizes that requiring parental consent for studies which involve the same risks as routine contraceptive care is discriminatory against adolescent participation. Patients who agree to participate will be randomized to the advance provision intervention (COCR) or to standard care (SC). Standard of care in our clinic is to tell all participants initiating the implant to call or follow-up if they have undesired side-effects. If they present with a complaint that is bleeding-related, they are told over the phone or in person that they have the option to try COCs for bleeding management. Those who desire COCs as an intervention are prescribed (over the phone) or given (in person) 3 packs of COCs. They are told to take one pill per day until the first pack is complete and save the remaining 2 packs for possible future use. Participants in the SC arm will be offered care according to our standardized protocol, which may include STI testing, reassurance and monitoring, prescription of COCs if desired, or removal. Participants in the COCR arm will receive three packs of combined oral contraceptive pills (35mcg ethinyl estradiol/norgestimate) and a specific protocol for their use for bothersome bleeding, as described below. We chose ethinyl estradiol/norgestimate because it is the main oral contraceptive pill that is provided in the family planning clinic through Title X governmental grant funding. Because we do not normally provide patients with pills at the time of implant insertion, Merck will cover the additional cost to the clinic for purchasing these pills. Participants in this arm may receive additional COCs as needed. Participants who receive COC's in any arm will be made aware of possible side effects of COC's including breast tenderness, headaches nausea, and bloating. Less common side effects could be related to mood or reduction in sexual libido. They will also be counseled on rare but more dangerous cardiovascular effects of combined contraceptive pills which increase increased blood pressure, venous thromboembolism and myocardial infarction or stroke. These risks are very low with the absolute risk of VTE in young women approximately 0.06 per 100 pill years (Solymoss S 2011). The risk of stroke in adolescents on combined oral contraceptive pills is 3.4 per 100,000 woman-years (Lidegaard 2012). The risks of VTE, MI and stroke in young woman on the pill are significantly lower than during pregnancy or the postpartum period.</p> <p>There is no clear recommendation for routine follow up visits after initiating combined hormonal contraceptives (USSPRCU Curtis KM 2016) but standard of care in the family planning clinic is to require a visit annually to monitor weight and blood pressure in order to continue use.</p> <p>All participants will be followed-up at 3 months, 6 months and one year by phone and/or online survey per participant preference. We will assess self-reported bleeding pattern, other side-effects, and overall satisfaction with the implant and with bleeding patterns. We will query the electronic medical record (Epic, Verona Wisconsin) to capture phone calls to clinic regarding the implant, appointments made related to the implant, and follow-up appointments attended. We will also assess use of COCs, implant discontinuation, and post-implant contraceptive method.</p> <p>We will also perform a similar medical record review to include people attending the clinic in the same time frame as the randomized trial who met inclusion criteria but were not enrolled in the study. This portion would be medical record review only and not include any contact with any patients.</p>
2.4 Study Flowchart	Please see study flowchart in section 2.5.
2.5 Study Procedures	This is an open-label randomized controlled trial. Participants will be recruited from the adolescent family planning clinic (BC4U) if they are new initiators of the

contraceptive implant. Participants will be eligible if they are 14-23.9 years old. Exclusion criteria will be any contraindications to estrogen containing birth control. We will obtain a waiver of parental consent as reproductive services are confidential in all adolescents in the state of Colorado.

We will use a pragmatic study design. When an order is placed in the EMR system (Epic), a message is generated to the provider to ask the patient about interest in participation, to review study procedures and inclusion and exclusion criteria. If the patient qualifies, the consent/assent document is generated, and the provider is asked to review and have the patient sign if she desires. All providers are HIPAA and GCP-certified. Participants will be automatically randomized by the EMR after consent, and study documents and instructions appropriate to the randomization group will be generated. We will use similar methods as those described in Curtis et al. This pragmatic study design is already in use in several protocols at University of Colorado Hospital. Providers will do all counseling for participants in either group. Participants in the COCR group will receive 3 packages of COC pills. They will be instructed to use the pills if their bleeding is bothersome AND it lasts more than 5 days. At day 6 of bleeding they should start the pills and take them daily until they finish the pack (21 active pills). If bleeding continues and is bothersome, they may begin the next pack of active pills. If bleeding stops, but then resumes at any time in the course of the study period and is bothersome to them they should start another pack. They can continue this throughout the time of their implant. They will be given refills on COC pills as needed. They may call and/or come into the clinic for follow up as desired. This information will be provided to the participants graphically, and at a 5th grade reading level.

Participants in the SC group will be counseled as usual on possible bleeding patterns with the implant. They will be told to call or follow up for any concerns with the implant, including bothersome bleeding. They will receive our clinic handout about the contraceptive implant.

We will obtain best and alternate phone numbers and email addresses. Each participant will be contacted by Dr. Richards, Dr. Teal, or the professional research assistant within 7 days of enrollment to confirm she has received any study supplies and understands her instructions.

Participants will be informed that we will contact them at 3, 6, and 12 months. At that time, we will offer a phone or online survey. We will make multiple attempts to contact them. We will also query the EMR for telephone calls and follow up appointments.

Participants will receive a \$25 gift card for initial study participation and a \$25 gift card for each follow up survey completed.

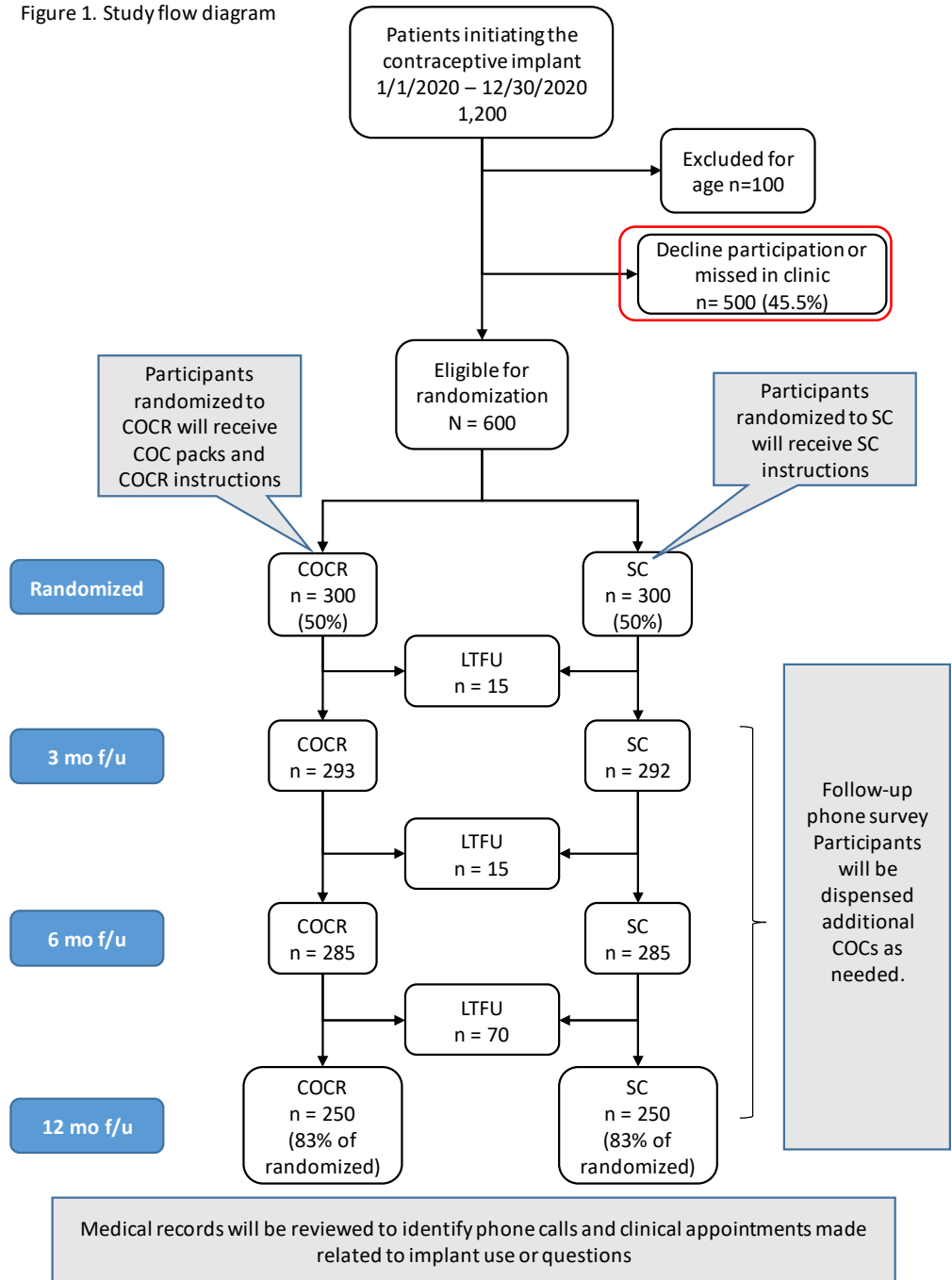
Participants from either group who would like their implant removed can come into clinic for removal. A standardized template will be used to document reason(s) for removal.

In the below flow diagram, all numbers are estimates based on our site's published and recent experience in patient volume, study participation, and follow-up rates.

We will also perform an identical medical records review for people who were not enrolled in the randomized trial (highlighted in the red box in the study flow diagram below) and will extract the variables highlighted in red below in the outcomes table. No other information will be examined for these patients.

We hypothesize that patients who are enrolled in the randomized trial and thus contacted by clinic staff after implant placement, are more likely to schedule follow-up visits to discuss bothersome bleeding patterns and less likely to have etonogestrel implant removed. The primary outcome for this secondary aim will be the number of appointments for breakthrough bleeding and implant removal.

Figure 1. Study flow diagram



2.6 Study Duration

We plan to enroll and randomize a total of 600 participants over a period of 12 months. We will follow all participants for up to 12 months post insertion. After completion of all study follow-up medical record review and data cleaning will take approximately three months.

2.7 Statistical Analysis and Sample Size Justification

Dr. Jeanelle Sheeder (Co-Investigator) will be responsible for analyzing the study data. This study is a non-blinded randomized controlled trial. Because this study involves standard clinical care, study arm will be identified in the electronic medical record and will be known to investigators and providers. However, no data will be aggregated or analyzed until study completion.

Variables:

The primary outcome variable will be retention of the contraceptive implant at 12 months post-insertion. Discontinuation will be determined through participant report at the 3, 6, and 12 month follow-up and by review of medical records.

Secondary outcome variables include:

Variable	Assessed by:
Satisfaction with bleeding profile	Likert scale ("very satisfied", "somewhat satisfied" and "not satisfied")
Satisfaction with method overall	Likert scale ("very satisfied", "somewhat satisfied" and "not satisfied")
Likelihood of recommending implant to a friend	Likert scale ("very likely," "somewhat likely" "not at all likely")
Follow up related to implant (visits or phone calls)	EMR review
Side effects attributed to implant	Phone/online survey

Additional variables include:

Variable	Assessed by:
Age	EMR
Race/Ethnicity	EMR
BMI	EMR

Statistical Methods

We will use standard bivariate statistics including Student's t-tests and non-parametric medians tests to compare continuous variables. We will use Chi-squared and Fisher's exact tests to compare dichotomous and categorical variables. The primary outcome will be analyzed using the Chi-squared test to generate an odds ratio and confidence intervals for continuation by study arm. Backwards stepwise logistic regression will be performed to identify independent predictors of implant discontinuation. In the first step, demographic variables will be included if they have a significant bivariate relationship to the outcome ($p < 0.1$). In the second step, each reproductive characteristic will be considered as a candidate predictor and included if it significantly ($p < 0.1$) improves upon the fit of the model from the first step. Study arm will be included in the third, final step. We will also compute estimates of time to discontinuation using Cox regression models.

Multiplicity

If necessary, we will use the Bonferroni method to correct for multiple comparisons.

Power/Sample Size:

Over the last 10 years BC4U clinic has placed approximately 1,200 implants per year. We anticipate that we will be able to enroll a total of 600 of the 1200 implant initiators (50%). Participants will be randomized in a 1:1 ratio. Thus, we will

	randomize 300 participants to each arm. Based on prior studies in this clinic (Richards 2017, Cohen 2017, Cohen 2019, Green 2019) , we hypothesize that 25% of participants in the SC arm will discontinue the implant within 12 months and 15% of participants in the COCR group will. With a loss-to-follow-up rate of 17% (from prior studies), we will have 80% power to detect this 10 percentage-point difference with a two-sided alpha of 0.05.
2.8 Specific Drug Supply Requirements	Nexplanons for this study will be purchased by BC4U clinic of Children's Hospital Colorado under the 340B program as per clinical standard of care. COCs for this study will be purchased by the BC4U clinic of Children's Hospital Colorado under the 340B program as per clinical standard of care. No drugs will be supplied by MSD.
2.9 Adverse Experience Reporting	We will use the Model Study Agreement reporting requirements for adverse events.
2.10 Itemized Study Budget	<i>A preliminary study budget must be provided with the initial proposal submitted to give guidance to the MISP Review Committee as to the expected study costs. A refined itemized budget detailing the costs associated with the study should be provided with the final protocol or included in the study agreement as Exhibit B.</i>
2.11 References	<p>Cohen R, Sheeder J, Teal S. Predictors of discontinuation of long-acting reversible contraception before 30 months of use by adolescents and young women. Journal of Adolescent Health. 2019 Aug. 65(2):295-302.</p> <p>Guiahi M, McBride M, Sheeder J, Teal S. Short-term treatment of bothersome bleeding for etonogestrel implant users using a 14-day oral contraceptive pill regimen: a randomized controlled trial. Obstet Gynec.2015;126(3): 508-513.</p> <p>Hou MY, McNicholas C, Creinin MD. Combined oral contraceptive treatment for bleeding complaints with the etonogestrel contraceptive implant: a randomized controlled trial. Eur J Contracept Reprod Health Care. 2016;21(5): 361-366</p> <p>Chen MJ, Hsia JK, Creinin MD. Etonogestrel implant use in women primarily choosing a combined oral contraceptive pill: A proof-of-concept trial. Contraception 2018;97(6):533-537.</p> <p>Phaliwong P, Taneepanich. The effect of mefenamic acid on uterine bleeding second to Implanon. J Med Assoc Thai. 2004;87(3):S64-8</p> <p>Cheng L, Zhu H, Wang A, Ren F, Chen J, Glasier A. Once a month administration of mifepristone improves bleeding patterns in women using subdermal contraceptive implants releasing levonorgestrel. Hum Reprod 2000;15:1969–72</p> <p>Weisberg E, Hickey M, Palmer D, et al. A pilot study to assess the effect of three short-term treatments on frequent and/or prolonged bleeding compared to placebo in women using Implanon. Hum Reprod.2006;21(1):295-302</p> <p>Simmons KB, Adelman AB, Fu R, et al. Tamoxifen for the treatment of breakthrough bleeding with the etonogestrel implant: a randomized controlled trial. Contraception. 2017;95(2):198-204</p>

	<p>Zigler RE, Madden T, Ashby C, et al. Ulipristal Acetate for Unscheduled Bleeding in Etonogestrel Implant Users: A Randomized Controlled Trial. <i>Obstet Gynecol.</i> 2018. 132(4):888-894</p> <p>Mansour D, Bahamondes L, Critchley H, et al. The management of unacceptable bleeding patterns in etonogestrel-releasing contraceptive implant users. <i>Contraception</i> 2011. 83(2):202-210</p> <p>Solymoss S. Risk of venous thromboembolism with oral contraceptives. <i>CMAJ.</i> 2011.183(18):E1278-9</p> <p>Lidegaard O, Lokkegaard E, Jensen A, et al. Thrombotic stroke and myocardial infarction with hormonal contraception. <i>N Engl J Med.</i> 2012;366(24):2257-66</p> <p>Curtis JR, Foster J, Saag KG. Tools and methods for real-world evidence generation: Pragmatic trials, electronic consent, and data linkages. <i>Rheum Dis Clin North Am.</i> 2019 May; 45(2): 275–289.</p> <p>Richards M, Teal SB, Sheeder J. Risk of luteal phase pregnancy with same-day initiation of subdermal contraceptive implants. <i>Contraception.</i> 2017 Apr;95(4):364-370.</p> <p>Cohen R, Sheeder J, Kane M, Teal SB. Factors associated with contraceptive method choice and initiation in adolescents and young women. <i>Journal of Adolescent Health.</i> 2017 Oct;61(4):454-460.</p> <p>Green S, Richards M, Sheeder J. Implant continuation in adolescents with bothersome bleeding with and without an intervention. <i>J Pediatr Adolesc Gynecol.</i> 2019; 32(2): 244-45.</p> <p>Green S, Richards M, Sheeder J. Factors associated with early removal of the etonogestrel implant for bothersome bleeding in adolescents. <i>J Pediatr Adolesc Gynecol.</i> 2019; 32(2): 201</p>
2.12 Publication Plan	<p>This study will be published as an original submission in a high-impact peer-reviewed journal. Preliminary considerations are: Obstetrics and Gynecology; the American Journal of Public Health; Journal of Adolescent Health; or Contraception. We anticipate at least two abstract presentations and two peer-reviewed publications from this data.</p> <p>The results will be submitted to the Society of Family Planning meetings in 2021 and 2022.</p>
2.13 Curriculum Vitae	See attached
2.13 Protocol Submission for Investigator-Initiated Studies	<p><i>U.S. protocols should be submitted by US investigators directly or through the Global Research Specialist at www.merckiiisp.com</i></p> <p><i>Non U.S. protocols should be submitted to the MSD office by the investigators.</i></p>