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INVESTIGATING THE PATTERNS OF ABNORMAL UTERINE BLEEDING IN WOMEN USING INTRAMUSCULAR DEPOT MEDROXYPROGESTERONE ACETATE, A COPPER INTRAUTERINE DEVICE OR A LEVONORGESTREL IMPLANT FOR CONTRACEPTION

Dr Natasha Di Rago (FCOG, BHSc , BHSc Hons, MBBCh)

Student number: 364575

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in Obstetrics and Gynaecology

Johannesburg, September 2025

Supervisors:

Dr Amy Wise- MBBCh, MMed(O&G), FCOG, Dip HIV Man, Cert MFM

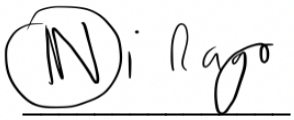
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I, **Natasha Chiara Di Rago**, Student number 364575, declare that this research report is my own work and that I contributed adequately to the findings in the article submitted. Assistance received has been acknowledged in the article. It is being submitted for the degree of Master of Medicine (MMed) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

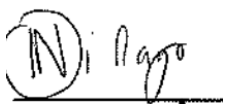
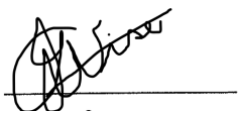
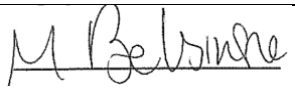
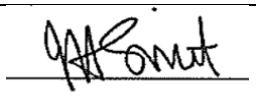


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Journal: BMC Public Health (submitted for consideration for publication). Submitted in submissible form.

Authors	Name	Signature
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2nd author	Amy Wise	
3rd author/ supervisor	Mags Beksinska	
4th author	Jenni Smit	

DEDICATION

I dedicate this MMed to my parents for working tirelessly to ensure that my sisters and I were educated at a tertiary level. I owe everything I have achieved to them.

ACKNOWLEDGEMENTS

I would like to thank the following people:

- Dr A. Wise for her guidance, expert opinion and ongoing support as my primary supervisor, also for assisting in arranging correspondence with the Wits MatCH Research Unit (MRU) and in doing so enabling this research.
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- Professor N. Pillay for patiently assisting with excel data sheets and guiding me through statistical analysis.

PRESENTATIONS

SASOG 2024, 41st National Congress of the South African Society of Obstetrics and Gynecologists, oral presentation, Sun City Convention Centre, 29/08/2024

Wits Faculty of Health Sciences Research Day and Postgraduate Expo 2024, Oral presentation, Wits Medical School, 05/09/2024

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SUBMISSIBLE ARTICLE

Patterns of abnormal uterine bleeding in women using intramuscular depot medroxyprogesterone acetate, a copper intrauterine device or a levonorgestrel implant for contraception: A sub-analysis of data from the ECHO randomised trial

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The Evidence for Contraceptive options and HIV Outcomes (ECHO)

Trial was a multi-center, open label, randomized clinical trial comparing HIV incidence and contraceptive benefits in women using depot medroxyprogesterone acetate (DMPA-IM), levonorgestrel (LNG) implants, and copper intrauterine devices (IUDs). FHI 360 Study #523201

ABSTRACT

Background: Access to contraception is a fundamental human right that significantly impacts women's health globally. In South Africa over 80% of women access contraception through the public sector and side effects, particularly abnormal uterine bleeding (AUB) remain a key reason for discontinuation. This sub-analysis aimed to evaluate changes in self-reported menstrual bleeding patterns across three contraceptive methods, to inform tailored counselling and improve continuation rates.

Methods: This sub-analysis utilized data from the ECHO trial, which was a multicentre randomized open-label study comprising of HIV-negative women seeking contraception across nine South African sites. Participants in the ECHO trial were randomized to receive depot medroxyprogesterone acetate (DMPA-IM), copper intrauterine device (IUD), or levonorgestrel (LNG) implant. From the original dataset of 5743 participants, 3026 (53%) had usable data—defined as complete responses on bleeding-related questions at both first visit (1 month of method use) and later visit (six months of method use). Self-reported menstrual changes were collected from standardized questionnaires completed during the trial and assessed for four domains: bleeding frequency, duration, volume, and subjective acceptability. Demographic variables (age, BMI, smoking status) were included. Categorical analyses were conducted using Pearson's chi-squared tests in R software; p-values <0.05 were considered significant.

Results: Group distribution was as follows: copper IUD (n=1595, 53%), LNG implant (n=870, 28%), and DMPA-IM (n=561, 19%). Statistically significant changes in bleeding patterns were observed between first visit and later visit across all methods ($p<0.001$). Copper IUD users most frequently reported prolonged and heavy bleeding, while LNG implant and DMPA-IM users more often reported infrequent, short, and lighter bleeding. Obese participants had significantly higher probabilities of infrequent (up to 58%),

prolonged, and light bleeding regardless of method. Smoking status was not significantly associated with any bleeding outcome. Among 323 participants who discontinued contraception, the most commonly cited reasons were heavy (29%) and prolonged bleeding (28%), followed by abnormal bleeding (26%) ($\chi 2=80.17$, df=4, $p<0.001$).

Conclusion: This study confirms that contraceptive related menstrual changes vary by method and user characteristics. While these findings support existing knowledge, the large sample size and South African setting offer important contextual insight into method specific bleeding patterns and their role in discontinuation. Understanding these changes can help providers deliver more individualized counselling. However, improved counselling alone may not fully address discontinuation if broader sociocultural perceptions of menstrual changes are not also addressed.

Keywords: Contraception, bleeding patterns, DMPA, intrauterine device, LNG implant, menstruation, counselling

LIST OF ABBREVIATIONS

AUB	Abnormal Uterine Bleeding
BMI	Body Mass Index
COC	Combined Oral Contraceptive
DMPA-IM	Intramuscular Depot Medroxyprogesterone Acetate
ECHO	Evidence for Contraceptive Options and HIV Outcomes
FIGO	International Federation of Gynaecology and Obstetrics
IUD	Intrauterine Device
LNG	Levonorgestrel
MRU	Match Research Unit

DECLARATIONS

Ethics approval

The ECHO Trial was approved by ethics committees at all the participating study sites [10] as well as the FHI 360 Protection of Human Subjects Committee. WHO approved the ECHO trial (ClinicalTrials.gov, no. NCT02550067). All participants gave written informed consent to participate in the trial. The protocol application for this subanalysis was approved in accordance with the Human Research Ethics Committee (Medical) at the University of the Witwatersrand, Johannesburg, reference M220416. Clinical trial number: not applicable

Consent for publication of article

Not applicable.

Availability of data and materials

The data that support the findings of this subanalysis of the ECHO Study are available from the corresponding author upon reasonable request. Access will be granted if the concept is evaluated to have scientific merit and if sufficient data protections are in place.

Competing interests:

The researcher and co-authors have no conflict of interest to declare.

Funding:

Funding for the ECHO Trial was provided by the combined support of the Bill & Melinda Gates Foundation, the American people through the United States Agency for International Development, the Swedish International Development Cooperation Agency, the South Africa Medical Research Council, and the United Nations Population Fund. Contraceptive supplies were donated by the Government of South Africa and the US Agency for International Development.

An application for funding from the Wits Masters of Medicine fund as well as to the South African Association of Trainees in Obstetrics and Gynaecology (SAATOG) research fund will be made to aid with publication fees.

Authors' contributions

ND conceptualised the study, conducted a literature search, collected and interpreted the data and drafted the initial manuscript. AW supervised the study, provided substantive revisions, and reviewed the manuscript. MB assisted with revisions, data acquisition and interpretation, and reviewed the manuscript. JS aided with data acquisition, review of manuscript, and final manuscript approval.

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INTRODUCTION

Globally, 214 million women living in developing regions are estimated to have unmet contraceptive needs [1]. Multiple factors act as barriers to contraceptive use, including poor access to healthcare, health concerns, and side effects [1]. Daily 810 women, of whom 94% are from low and middle-income countries, die from preventable complications of pregnancy and childbirth [1]. In the global Safe Motherhood Initiative, family planning has been outlined as one of the six "pillars" of safe motherhood [2]. One of the solutions to attempt decreasing maternal mortality is to increase the uptake of contraceptives [2]. A study done by Kriel et al. in Kwa-Zulu Natal, a province in South Africa, found that major barriers still exist in the quality of care that users of public health contraceptive services receive [3]. It highlighted the limited choice of contraceptives given to women and the lack of autonomy in choice of

method. It was found that inadequate counselling, information, and fear were factors responsible for reduced follow-up and continuation of contraceptive services [3].

It is well documented that different contraceptive methods have varying side effects which are largely user specific, with certain contraceptives better tolerated than others. Improved education regarding the role of contraceptive methods on menstrual cycle disturbances may lead to increased contraceptive uptake and compliance and ultimately decrease the incidence of unwanted pregnancies and their sequelae.

Worldwide the prevalence of obesity has almost tripled in the last four decades, resulting in more women of reproductive age having an increased body mass index (BMI) [4]. It is therefore necessary to consider BMI when selecting an appropriate contraceptive method.

Cigarette smoking has been associated with anti-estrogenic effects, which may result in lowered estrogen levels [5]. In the general population, abnormal uterine bleeding (AUB) is more commonly observed among smokers, likely due to the effects of smoking and nicotine on the endometrial lining. Research indicates that smokers are, on average, 47% more likely to experience AUB compared to non-smokers, independent of contraceptive use [6]. .

Studies on contraceptive discontinuation have shown users' perception of and experience with side effects to be a strong influence in their decision to stop contraception despite still requiring it [7]. As cited by Ali, Cleland and Shah, the World Health Organization (WHO) found after reviewing several demographic and health surveys that method-related concerns including experience of side effects (especially bleeding disturbances, weight gain, and headaches), dissatisfaction with the method's impact on menstruation or libido, and concerns about long-term health risks and infertility was the highest reason for discontinuation across all contraceptive methods [8].

A qualitative study performed in South Africa in 2019 found that numerous factors impact women's experiences related to contraceptive uptake, initiation and continuation [9]. Menstrual cycle changes including intermenstrual bleeding and amenorrhea were regular reasons for change of method, or discontinuation [9].

While barriers to contraceptive use remain a significant issue in South Africa, this study focuses on understanding the menstrual changes associated with commonly used contraceptive methods. These changes may include alterations in bleeding frequency, duration, volume, and overall acceptability—side effects that can strongly influence method continuation. Additionally, individual factors such as body mass index (BMI) and smoking status may affect the nature and severity of these menstrual changes. This study aims to characterize and compare self-reported menstrual pattern changes among users of the copper IUD, DMPA-IM injection, and LNG implant over a six-month period, with a view to supporting more personalized and informed contraceptive counselling.

METHODS

Study Design and Setting: This study was a secondary, cross-sectional analysis of data derived from the Evidence for Contraceptive Options and HIV Outcomes (ECHO) trial (ClinicalTrials.gov Identifier: NCT02550067), a multicenter, randomized, open-label study conducted across four Africa countries. The ECHO trial aimed to evaluate HIV acquisition risk among women using three contraceptive methods. For this subanalysis, we examined data specifically from the South African cohort, which included participants recruited from nine healthcare facilities in both urban and peri-urban settings: Brits, Cape Town, Durban, East London, Edendale, Johannesburg, Klerksdorp, Ladysmith, and Soshanguve. The trial was conducted between December 2015 and September 2017.

Ethical consideration: Ethical approval was sought and granted by the Human Research

Ethics Committee (HREC) of the University of the Witwatersrand. (Clearance certificate number M230141) and local research ethics committees for each of the study sites (Protocol Appendix D) as well as the FHI 360 Protection of Human Subjects Committee. The WHO approved the ECHO study (ClinicalTrials.gov, no. NCT02550067, registered on September 16, 2015).

Study Population: Participants from the ECHO study were HIV-negative women aged 16–35 years seeking contraception. Participants included women who met the trial criteria set out by the inclusion criteria of the ECHO consortium (Protocol Appendix J). All were randomized to receive one of three methods: the copper intrauterine device (IUD), depot medroxyprogesterone acetate intramuscular injection (DMPA-IM), or the levonorgestrel (LNG) implant. All participants had been off hormonal contraception prior to enrolment, ensuring that menstrual changes reflected the new method initiated in the study.

To be included in this subanalysis, participants from the dataset needed to have completed bleeding-related questionnaires at both the first visit (within one month of initiation) and a follow-up visit (within six months). Women with secondary amenorrhea at follow-up were excluded, as they could not complete bleeding-related questions.

Of the 5,743 South African participants, **3,026** (53%) had complete and usable data. “Usable data” was defined as complete responses to four key questions on bleeding patterns (frequency, duration, volume, and acceptability) at both time points. The reduced sample size was primarily due to some participants in the Levonorgestrel (LNG) implant and Depot Medroxyprogesterone Acetate (DMPA-IM) group developing secondary amenorrhea, which prevented them from responding to questionnaire items related to bleeding patterns, questions 13- 16 (Protocol Appendix A)”

Variables and Data Collection: Bleeding patterns were self-reported through standardized Case Report Forms (CRFs), administered by trained personnel in the participant's preferred language. Questions assessed included bleeding frequency (about right, infrequent, too frequent), bleeding duration (about right ,too short, too long, volume of blood loss (about right, too little, too much) and overall acceptability of bleeding (acceptable, not acceptable). These variables were treated as categorical outcomes. Participants who fell within a BMI category of 30 upwards were classified obese, those below as normal. Participants who smoked any number of cigarettes from one upwards per day were considered smokers. Independent variables included contraceptive method, body mass index (BMI: obese vs. normal), and smoking status (yes/no).

Statistical Analysis: Descriptive statistics summarized participant characteristics and responses. Pearson's chi-squared tests were used to assess associations between contraceptive method and bleeding outcomes. Standardized residuals identified specific response patterns contributing to significant results. Multinomial logistic regression was used to evaluate the influence of BMI and contraceptive method on bleeding outcomes, due to the categorical nature of the dependent variables. Smoking status was excluded from regression due to limited significance in univariate analysis. All statistical analyses were performed using R (version 4.0.0), with significance set at $p<0.05$.

RESULTS

The derivation of the final sample size is illustrated in Figure 1. The sample size included more patients in the copper IUD group (n=1595; 53%); followed by LNG implant (n = 870, 28%), and DMPA-IM (n = 561, 19%) (χ^2 = 558.58, df = 2, $p < 0.001$). The smaller sample numbers in the DMPA-IM and LNG implant groups are attributed to the development of secondary amenorrhea in some patients, a common side effect of progesterone-containing devices, which led to exclusion from the analysis.

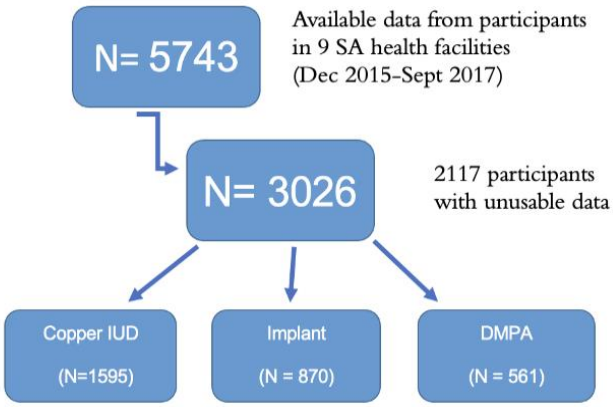


Figure 1: Flow chart illustrating the derivation of the final population sample size

Frequency

Figure 2 shows the proportions of participants on the three contraceptive methods and their frequency of bleeding, recorded at their first visit and six months later at their later visit.

The relationship between the type of contraceptive and frequency of bleeding was statistically significant for the first ($\chi^2 = 38.66$, df = 4, $p < 0.001$) and later visit ($\chi^2 = 193.83$, df = 4, $p < 0.001$) (Figure 2). For both visits, most patients considered bleeding frequency for all three contraceptives about right. An examination of the standardized residuals indicated that for the first visit there was a relatively higher contribution (0.23) of too frequent bleeding for the copper IUD (20% n=319). For the later visit, infrequent bleeding for DMPA-IM (24% n=134) had a relatively higher contribution (0.88) to the outcome, indicating that this specific group influenced the overall test result more than others, suggesting that the observed frequency of bleeding differs meaningfully from the expected pattern. Notably, a significant number of participants in the LNG implant group (20% n=174) also reported infrequent bleeding at the later visit.

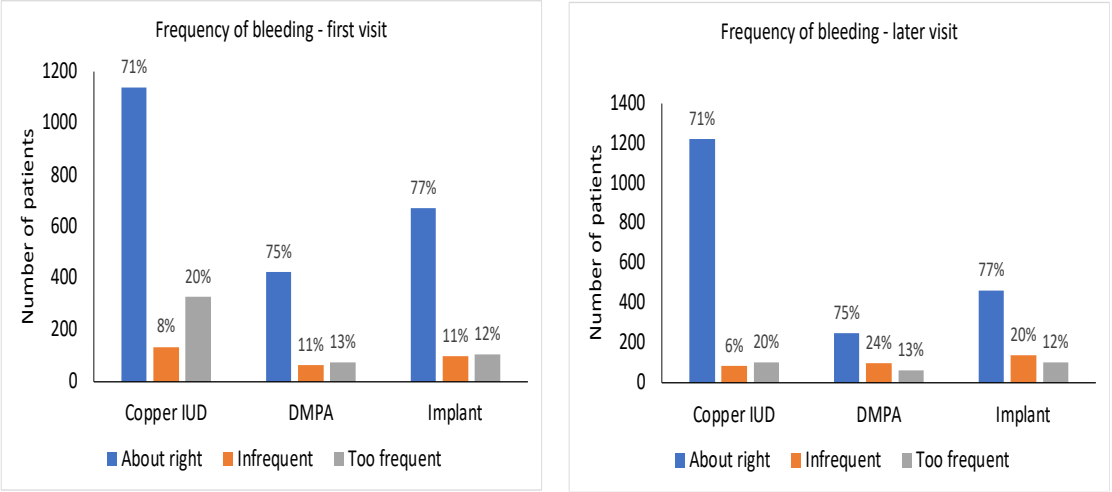


Figure 2: Self-reported opinion of bleeding frequency by contraceptive group at first and later visit

Duration

The counts of participants using the three contraceptive methods and their duration of bleeding, recorded at their both their first and later visit, are displayed in Figure 3. The relationship between the type of contraceptive and duration of bleeding was statistically significant for both the first (χ^2 = 36.22, df = 4, $p < 0.001$) and later visit (χ^2 = 170.03, df = 4, $p < 0.001$). At both time points, most participants considered duration of bleeding in all three contraceptives to be about right, although the copper IUD also had a notable proportion of participants (36% n=574) reporting bleeding duration to be too long at the first visit.

Bleeding was reported as too short in a relatively high number of participants from the DMPA-IM group at both the first and the later visit (11% n=61), and by the LNG implant group at their later visit (11% n=95).

An examination of the standardized residuals indicated a relatively higher contribution (0.49) of a short duration of bleeding among DMPA-IM users for the first visit, and an even higher contribution (0.72) among LNG implant users at the later visit. A higher contribution in this context indicated that the observed number of participants reporting short bleeding duration in the DMPA-IM group differed more from what would be expected under the assumption of

no association between contraceptive type and bleeding duration. This group therefore played a larger role in driving the statistically significant result, suggesting short bleeding duration was particularly characteristic of DMPA-IM users at the first visit and LNG implant users at the later visit.

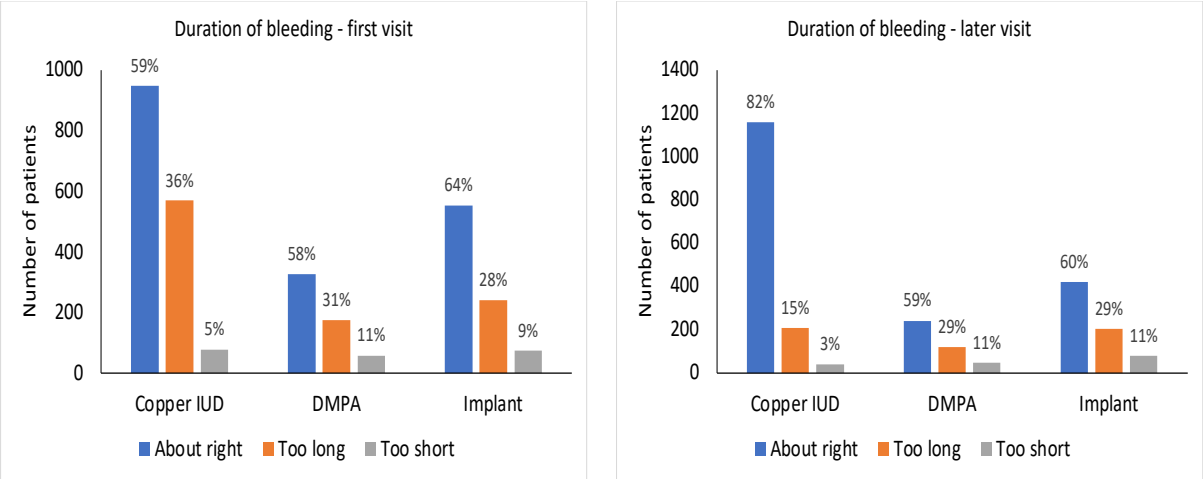
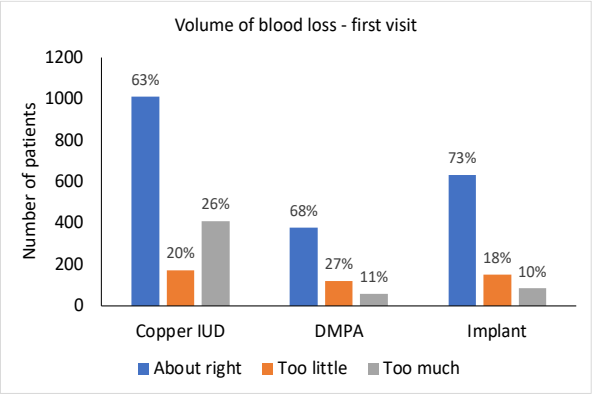


Figure 3: Self-reported opinion on duration of bleeding by contraceptive group at first and later visit

Volume

The relationship between the type of contraceptive and volume of bleeding was statistically significant for both the first (χ^2 = 146.54, df = 4, p < 0.001) and later visit (χ^2 = 150.77, df = 4, p < 0.001). As shown in figure 4, for both visits, most participants considered volume of blood loss for all three contraceptives about right. For the copper IUD group (n=1595) a substantial number of participants reported volume of blood loss to be too much at both the first (26% n=414) and later visit 14% (n=223). Participants in the DMPA-IM group reported too little bleeding at both the first (27% n=70) and second visit (22% n=123). The LNG implant group also showed high proportions of too little bleeding at the first and later visit (18% n=156 and 17% n=147), respectively. An examination of the standardized residuals indicated a relatively higher contribution (0.40) of too much bleeding for the copper IUD for the first visit, and too little bleeding (1.11) for the DMPA-IM at the later visit.



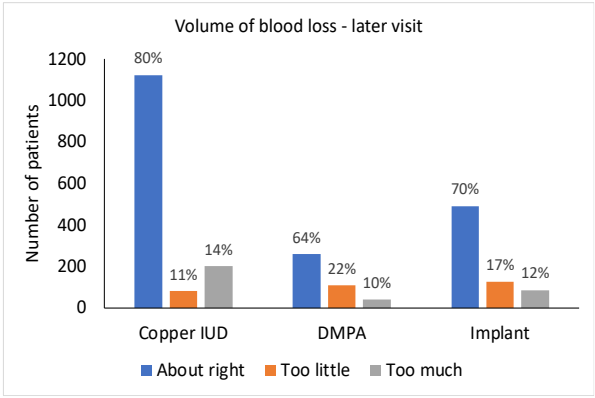


Figure 4: Self-reported acceptability of volume of blood loss by contraceptive method at first and later visit

Opinion of bleeding pattern

The relationship between the type of contraceptive used and their opinion of bleeding was statistically significant for both the first (χ^2 = 69.31, df = 2, p < 0.001) and later visits (χ^2 = 21.97, df = 2, p < 0.001). Figure 5 shows that at both visits, the majority of participants found bleeding associated with all three contraceptive methods to be acceptable. In the copper IUD group, 19% (n=303) of participants considered bleeding to be not acceptable at their first visit, whereas higher proportions of participants in the DMPA (22% n=123) and LNG implant (22% n=191) groups found bleeding to be unacceptable at their later visit.

An examination of the standardized residuals provided further insight into the observed patterns of bleeding acceptability. At the first visit, copper IUD users had a residual contribution of 0.20 in the "not acceptable" category, indicating a slightly higher number of participants reporting unacceptable bleeding than would be expected under the assumption of no association between contraceptive method and bleeding acceptability. At the later visit, DMPA-IM users showed a higher contribution of 0.55 in the "not acceptable" category, suggesting that a substantially greater proportion of participants in this group found their bleeding unacceptable compared to what was expected. This deviation contributed meaningfully to the overall association between contraceptive method and perceived bleeding acceptability, highlighting that DMPA-IM users at the later visit were more likely than users of the other methods to report bleeding as not acceptable.

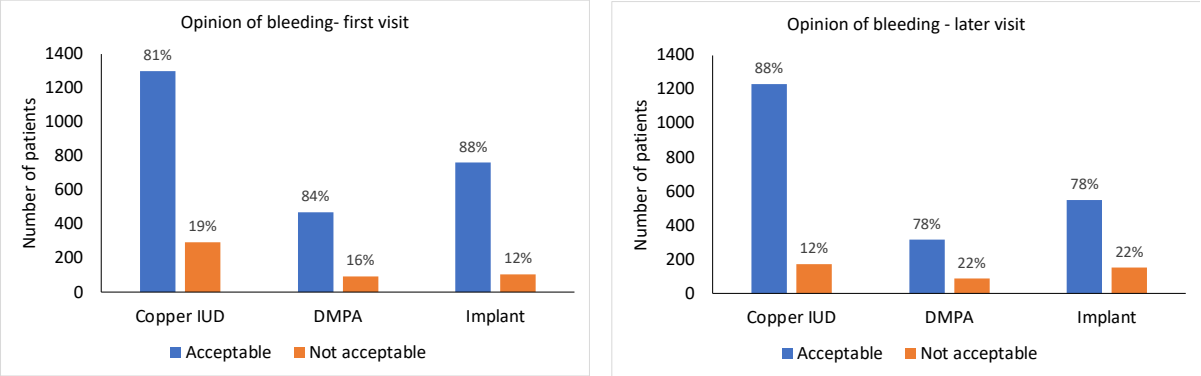


Figure 5: Acceptability of bleeding pattern by contraceptive method at first and later visit

The role of obesity in bleeding patterns whilst on contraceptives

The probabilities of obesity affecting bleeding frequency, duration, volume, and opinion are shown in Table 1 to Table 4. When considering the role of obesity in bleeding frequency, Table 1 demonstrates that women with a normal BMI had a high probability (+/- 85%) of reporting that their bleeding frequency was about right. In contrast, among women classified as obese, the probability of reporting infrequent bleeding was higher (approximately 55–58%) than in those with normal BMI, indicating a tendency toward less frequent bleeding in this group.

Table 1: Probabilities of obesity effecting frequency of bleeding

Contraceptive Method	Obesity Status	About right	Infrequent	Too frequent
Copper IUD	Obese	0.38	0.55	0.07
Copper IUD	Normal	0.85	0.0	0.13
DMPA	Obese	0.38	0.55	0.07
DMPA	Normal	0.85	0.02	0.13
Implant	Obese	0.36	0.58	0.06
Implant	Normal	0.86	0.02	0.12

Table 2 shows that, regardless of contraceptive method, obese participants had approximately 72% greater chance of experiencing a long duration of bleeding compared to

women with a normal BMI. In contrast, women with a normal BMI had significantly higher odds of reporting their bleeding duration as “about right.”

Table 2: Probabilities of obesity effecting duration of bleeding

Contraceptive Method	Obesity Status	About right	Too long	Too short
Copper IUD	Obese	0.27	0.71	0.02
Copper IUD	Normal	0.87	0.04	0.09
DMPA	Obese	0.25	0.73	0.02
DMPA	Normal	0.87	0.05	0.09
Implant	Obese	0.25	0.73	0.02
Implant	Normal	0.86	0.05	0.09

Regarding volume of blood loss, Table 3 shows that women with normal BMI consistently showed a higher probability (77-80%) of "About right" volume of blood loss compared to obese participants who showed a higher probability (49-68%) of "Too little" blood loss.

Table 3: Probabilities of obesity effecting volume of bleeding

Contraceptive Method	Obesity Status	About right	Too little	Too much
Copper IUD	Obese	0.42	0.49	0.09
Copper IUD	Normal	0.80	0.03	0.16
DMPA	Obese	0.41	0.50	0.10
DMPA	Normal	0.79	0.03	0.18
Implant	Obese	0.26	0.68	0.06
Implant	Normal	0.77	0.07	0.16

Table 4 examined the effect of obesity status on opinions of bleeding volume. The statistical model did not converge, indicating that stable parameter estimates could not be obtained. Consequently, no statistically significant difference was detected between obese and normal BMI groups. This suggests that within the dataset, obesity status did not have a measurable effect on perceptions of bleeding.

Table 4: Probabilities of obesity effecting opinion of bleeding

Contraceptive Method	Obesity Status	Acceptable	Not acceptable
Copper IUD	Obese	2	0
Copper IUD	Normal	0	2
DMPA	Obese	2	0
DMPA	Normal	0	2
Implant	Obese	2	0
Implant	Normal	0	2

Effect of smoking on bleeding patterns

Figure 6 shows the relationship between the occurrence of smoking and bleeding patterns in the study. The dataset comprised a total of 198 smokers and 2828 non-smokers.

Generally, both smoking and non-smoking participants said their bleeding patterns were about right. Within the smoking group, 17% (n=33) of participants reported frequency of bleeding to be too frequent, 32% (n=63) too long and 18% (n=35) reported volume of blood loss to be too much. However, of the participants who smoked, 84% (n=166) felt their bleeding pattern was acceptable.

Smoking was not significantly associated with frequency of bleeding (χ^2=1.98, df=2, p=0.371), duration of bleeding (χ^2=2.10, df=2, p=0.350), volume of bleeding (χ^2=0.40, df=2, p=0.817), and opinion of bleeding (χ^2=0.00, df=1, p=1.000).

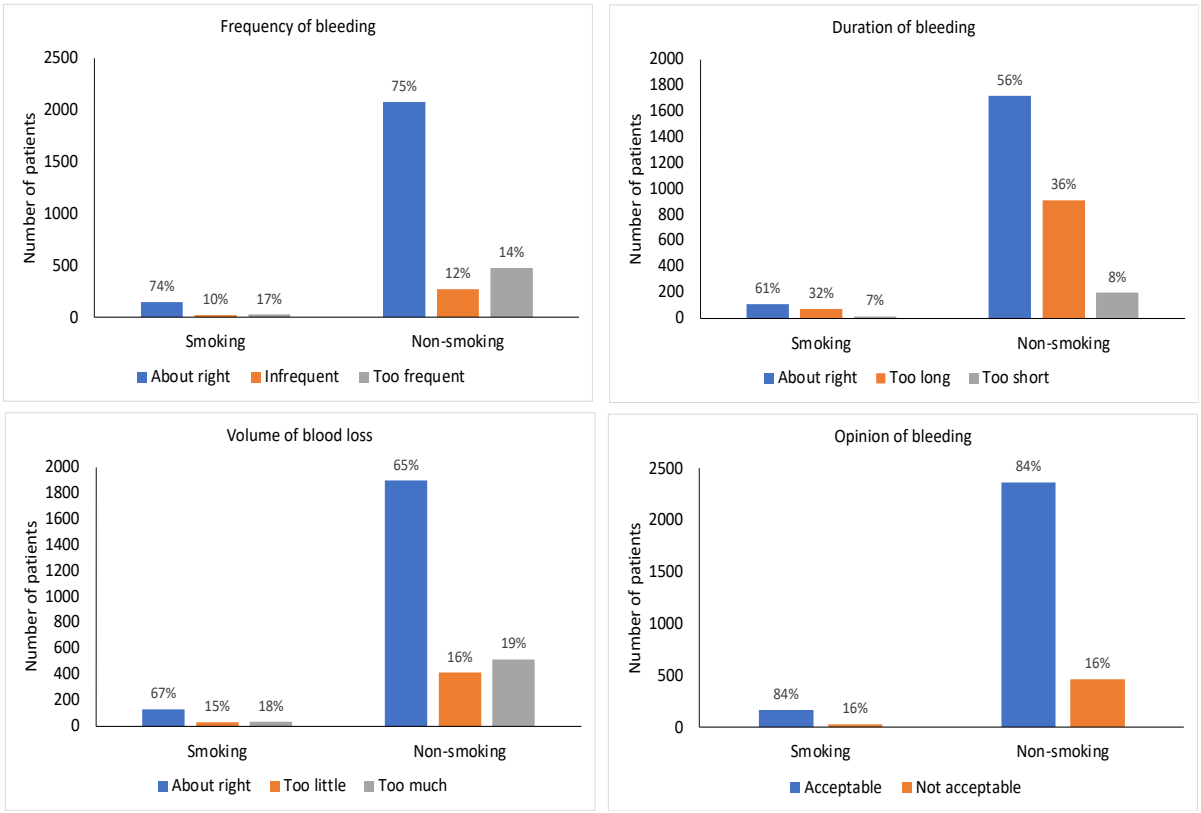


Figure 6: The relationship between smoking and bleeding patterns recorded at first and later visit

The role of bleeding in discontinuation of contraceptive method

Data on the role of AUB in contraceptive discontinuation were available for 323 participants who had discontinued their contraceptive method. Of these, there was a graded response in the role of bleeding on discontinuation across all three methods. This is demonstrated in table 5, with the most common reasons for discontinuation of contraceptive being heavy menstrual bleeding (n=95, 29%), prolonged menstrual bleeding (n=91, 28%), and abnormal uterine bleeding (n=85, 26%). These percentages were significantly greater than those for participants with irregular menstrual bleeding and amenorrhea (χ^2=80.17, df=4, p<0.001).

Table 4: Bleeding patterns most associated with discontinuation of contraceptive method across all three methods

Abnormal uterine bleeding	85	26%
Amenorrhea	17	5%
Irregular menstrual bleeding	35	11%
Heavy menstrual bleeding	95	29%
Prolonged menstrual bleeding	91	28%

The relationship between bleeding patterns and cassation of contraceptive method is further demonstrated in figure 7 in a graphical format.

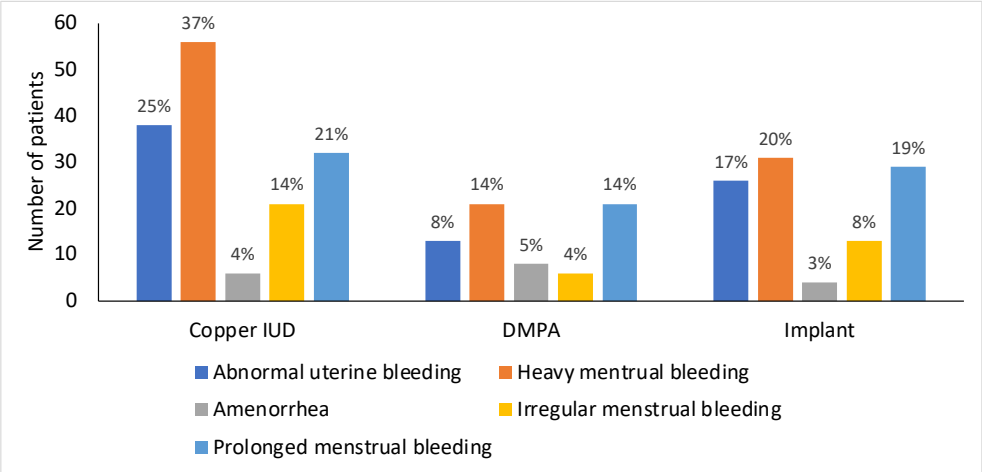


Figure 7: The relationship between cessation of contraceptive method and different bleeding patterns

DISCUSSION

Irregular menstrual bleeding has been shown to be the most common clinical side effect causing discontinuation of contraceptive method [11]. Objective assessment of bleeding patterns is therefore crucial in the evaluation of a contraceptive method to ensure its ongoing use and acceptance. This study focused on characterizing the differences in iatrogenic AUB amongst three modes of contraceptives.

In the examination of bleeding patterns among copper IUD users, 20% of participants expressed concern regarding the frequency of bleeding, with 36% reporting duration of bleeding as a point of concern during their initial visit. Volume of blood loss was similarly reported as too much in 26% of participants, and bleeding pattern overall was considered unacceptable in 19% of users at their first visit.

These findings mirror existing research where intermenstrual spotting and prolonged and heavy menstrual bleeding are reported to be common side effects in copper IUD users, this being one of the leading reasons for method discontinuation [12]. This is likely secondary to the copper IUD causing a sterile inflammatory response within the uterus, rendering it

inhospitable to sperm [13]. This inflammation can lead to heavier bleeding than normal. A meta-analysis by the Indian Council of Medical Research found that use of the copper IUD was associated with increased frequency of bleeding in 18-20% of users, particularly within the first three months of use [11].

Regarding bleeding patterns in DMPA-IM users in our study; 24% of participants reported infrequent bleeding at their later visit. At both the first and second visits the duration of bleeding was considered too short, and the volume of blood loss was reported as too little by 27% of participants at their first and 22% at their later visit.

Twenty percent of participants assigned to the LNG implant group reported infrequent bleeding and described the duration of bleeding to be too short at the later visit. The implant group also showed high proportions of too little bleeding at both first and later visits. In both the DMPA-IM and Implant groups, 22% of participants found bleeding to be unacceptable at their later visit.

Considering the above, it is not surprising that bleeding patterns for DMPA-IM and LNG Implant groups were similar. Research conducted in India showed infrequent bleeding to be common in users of Norplant II (a hormonal long acting implant) as well as those using injectable contraceptives [11]. These findings illustrate the difference in bleeding patterns with use of hormonal contraceptives (the implant and DMPA-IM) versus non-hormonal methods (the copper IUD).

Hormonal implants contain progestin, preventing pregnancy by suppressing ovulation and thickening cervical mucosa. DMPA-IM works similarly by suppressing ovulation and follicular development, with the lower oestrogen state leading to inhibition of endometrial thickening [13]. Understanding the mechanism of action of hormonal methods makes it easier to explain why bleeding patterns were altered, specifically at later visits when hormones had been given adequate time to exert their effects.

Although hormonal methods have a propensity to cause less bleeding frequency, shorter duration, and volume of blood loss in both groups, these patterns were reported as unacceptable by participants of our study. A unique descriptive study in South Africa reported that contraceptive choices are often influenced by wider social networks and local knowledge, with changes in menstrual cycle being most often the reason for change or discontinuation of method [14]. While amenorrhea or reduced bleeding is considered a desirable or convenient side effect in some cultural contexts, in this setting it was commonly perceived as unnatural or indicative of underlying illness. These culturally rooted perceptions highlight the importance of understanding local beliefs and menstrual norms when introducing contraceptive methods in similar African communities [14].

The analysis of bleeding patterns across different contraceptive methods revealed notable associations with obesity status. Overall, obese participants were more likely to report experience of infrequent bleeding, prolonged bleeding duration, and reduced volume of blood loss compared to those with a normal BMI, regardless of the type of contraception used. These findings suggest that obesity may independently influence bleeding profiles in users of contraception, potentially compounding or modifying the effects of specific contraceptive methods.

Various studies have illustrated that the increased rates of menstrual cycle disturbance in high BMI patients (25- 40 or greater) primarily related to the effects of obesity on gonadal steroid hormone concentration, leading to the disruption of normal ovulation and dysfunctional uterine bleeding [7]. With the increasing prevalence of obesity worldwide, the importance of considering BMI when selecting an appropriate method of contraceptive is paramount. The American College of Obstetricians and Gynecologists highlights the safety and efficacy of intrauterine devices (IUDs) as contraceptive options [15]. Furthermore, according to the WHO Medical Eligibility Criteria, both the levonorgestrel (LNG) implant and

the copper IUD are classified as category 1 methods for individuals with a BMI ≥30, indicating that they are safe and suitable for use in this population [16].

When analyzing the effect of smoking on bleeding patterns, the main limitation was the small sample size of only 7% of the sample (n=198). However, within the smoking group, 17% of participants reported bleeding to be too frequent, 32% too long, and 18% reported volume of blood loss to be too much. Eighty-four percent felt their bleeding pattern was acceptable. Smoking was not significantly associated with frequency, duration, volume, or opinion of bleeding. Although the findings were not significant in this study's limited sample, evidence from the general population shows that smokers are 47% more likely to experience AUB compared to non-smokers [6]. The cause of AUB in smokers is likely to be related to the effect of smoking and nicotine on the endometrium. Smoking inhibits the growth of new blood vessels, with nicotine promoting local angiogenesis. These changes in standard physiology interfere with the ordinary course of cell growth within the endometrium, leading to disorganised cellular events that result in uneven shedding of the endometrial lining and irregular bleeding [17].

Data pertaining to the role of AUB on the discontinuation of contraceptive methods were available for 323 participants. The most common reasons for discontinuation of contraceptive method were heavy bleeding, followed by prolonged bleeding across all three methods of contraceptives.

A review article including 54 studies on contraceptive discontinuation have shown users' perception of and experience with side effects to be a strong influence in their decision to stop contraception, despite still requiring it [18]. The role of client-provider interaction in contraceptive discontinuation was explored in the article. The importance of optimizing contraceptive counseling was highlighted as a means of supporting clients to choose methods that will enable voluntary continuation [18]. The article also emphasized the

importance of information exchange during counseling to prepare clients for side effects. It concluded that providers should consider using more evidence-based counseling approaches as part of a strategy for decreasing method-related discontinuation of contraception [18].

LIMITATIONS

This was a sub-analysis of a larger study, the ECHO study, which had different aims to those sought by this sub-analysis. Missing data from certain participant questionnaires led to exclusion from the analysis. Another limitation was the smaller sample sizes in the DMPA-IM and LNG implant groups. This was primarily because some participants using these hormonal contraceptive methods developed secondary amenorrhea, which prevented them from responding to all questions related to bleeding abnormalities. As a result, their incomplete questionnaires led to their exclusion from the analysis. The sample size for the smoking group included only 7% of the total sample, therefore results in this limited sample were found not to be significant.

A further limitation of this study is the reliance on self-reported data collected through questionnaires to assess bleeding patterns, including frequency, volume, duration and opinion of blood loss. While these subjective measures provide useful insights, they are inherently limited by recall bias and variability in individual interpretation. Objective measures such as menstrual calendars, detailed recording of the number of bleeding days, episodes of overflowing, pad usage (e.g., number of pads used per day) or menstrual volume measurements—would have provided more accurate and quantifiable assessments of abnormal bleeding. The lack of such objective data limits the precision with which bleeding abnormalities could be evaluated in this study.

RECOMMENDATIONS

- This study emphasises the importance of counseling and shared decision-making between healthcare workers and patients around contraceptives, and what to expect from their chosen method.
- Bleeding side effects should be addressed, and ongoing follow-up and management should occur.
- More prospective studies need to be done in South Africa to better understand the effect of contraceptive side effects on method discontinuation, and how these can be managed best.

CONCLUSION

This research highlights the impact of different contraceptive methods on bleeding patterns. It depicts how each method influences bleeding patterns, specifically within one month of use and approximately six months later. Equipped with this knowledge, healthcare workers can adopt a more comprehensive counselling approach, enabling patients to select contraceptives appropriate to their specific need, thereby leading to increased compliance and continuation rates and an overall improvement in contraceptive outcomes.

DISCLOSURE

The authors report no conflict of interest in this study.

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APPENDICES

Appendix A: Approved Research Protocol

1 Introduction

1.1 Background

Access to contraception forms a fundamental role in human rights and contributes to improved health outcomes. Globally, 214 million women living in developing regions are estimated to have unmet contraceptive needs (1). Multiple factors act as barriers to women needing contraceptives including; poor access to healthcare, health concerns, side effects and lack of power in decision making within relationships (1).

Daily 810 mothers, of which 94% are from low and middle income countries, die from preventable complications of pregnancy and childbirth (1). Family planning has been outlined as one of the six “pillars” of safe motherhood in the global Safe Motherhood Initiative (2). One of the solutions to attempt to decrease maternal mortality is to increase the uptake of contraceptives; this in turn will improve child survival by promoting intentional timing and spacing of pregnancies(2).

In South Africa (SA), it is estimated that 83% of women who require contraceptive services access it through the public health sector (3). Teenage pregnancies; defined as pregnancies in the age category 15-19 years; are increasing significantly, with 16% of teenagers commencing child bearing. The mean age of first pregnancy in South Africa is 21 years old (3).

Quality of care in relation to family planning is defined as the quality of contraceptive methods, attitudes of health care staff and contraceptive outcomes (3). A study done by Kriel et al. in KZN found that major barriers still exist in the quality of care that users of public health contraceptive services receive. The study showed that women have limited choice of contraceptives and are not given autonomy in choosing a method. It was found that lack of counselling, inadequate information and fear were factors responsible for reduced follow up and continuation of contraceptive services (3).

It is well known that different contraceptive methods have varying side effects, and side effects are patient specific, with certain contraceptives being better tolerated than others depending on patient factors. Discontinuation of contraceptive methods is often attributed to undesirable side effects. Improved patient education surrounding the role of contraceptive methods on menstrual cycle disturbances, may lead to increased contraceptive uptake, compliance and ultimately decrease the incidence of unwanted pregnancies and its sequela.

1.2 Abnormal Uterine Bleeding

The term Abnormal uterine bleeding (AUB) was first introduced by the International Federation of Gynaecology and Obstetrics (FIGO) Menstrual Disorders Working Group in 2011 (4).

FIGO classified the underlying causes of AUB in reproductive years using the PALM-COEIN method, which was revised in 2018 and is based on structural and non-structural causes of AUB (5).

AUB is defined as any change in the duration, volume, frequency and regularity of uterine bleeding. It also includes intermenstrual bleeding and unscheduled bleeding when using varying types of hormonal preparations or intra-uterine devices (IUD) (5).

Structural causes can be imaged or examined using histopathology (Polyps, Adenomyosis, Leiomyomas and Malignancy or atypical endometrial hyperplasia; PALM). Non-structural causes include those diagnosed by clinical assessment, detailed history, physical exam and occasionally laboratory testing (Coagulopathies, Ovulatory disorders, primary Endometrial disorders, Iatrogenic and Not otherwise classified; COEIN) (5).

Multiple studies have shown iatrogenic AUB (AUB I) to be a major cause for contraceptive discontinuation(6)AUB I forms part of the non-structural causes of AUB and encompasses abnormal bleeding caused by systemic pharmacotherapy or intrauterine systems. This group includes gonadal steroids such as oestrogen, progestins and androgens and substances that affect their production and function. It also includes pharmaceuticals that may cause to ovulatory disorders, for example those affecting dopamine metabolism like phenothiazines and tricyclic anti-depressants (5).

1.3 Contraceptive methods

Contraceptive methods can be divided into three main groups: short acting contraceptives, long acting reversible contraceptives (LARC) and permanent.
Short-acting contraceptives, are methods which require regular use or use within short time intervals ranging from single use, daily use, and up to three monthly (examples include; condoms, spermicides, pills, hormonal rings, patches and injectable's) (7)

Long-acting reversible contraceptives (LARC), defined as methods lasting three or more years include; IUD's and hormonal implants. Randomised open label trial Permanent methods include sterilization (7).

A major advantage of LARC's is that once initiated they do not require active adherence (7). Unlike other short acting methods that are user-dependent, LARC methods only require intervention once they need to be discontinued (7).

Two different methods of LARC's will be explored in this study namely the copper IUD and the levonorgestrel (LNG) implant. The copper-containing IUD induces a sterile inflammatory response in the uterus, making it inhospitable to sperm (7). Additionally, the copper IUD is the most effective form of emergency contraception and may be used within 10 days of unprotected intercourse (7).
LNG implant is a rod containing progestin that is inserted sub-dermally into the upper arm. It prevents pregnancy by altering the viscosity of cervical mucous and suppressing ovulation (8).

Intramuscular depot medroxyprogesterone acetate (DMPA-IM) is a short acting contraceptive. DMPA suppresses ovulation and follicular development; the resulting lower oestrogen state causes thinning of the endometrium.

The contraceptive CHOICE project of 2010, with a cohort of 10, 000 women, found that two thirds of participants chose to use LARC's once financial barriers were removed(9). This pioneer study was the precipitant for the promotion and advocation of use of LARCS in women of reproductive age. The updated National Institute for Health and Care Excellence (NICE) guidelines of 2019, further state that all currently available forms of LARC's are more cost effective than injectable contraceptives and are cheaper to use than the combined oral contraceptive methods even after 1 year of use (9). In a review article by members of the Brazilian National Specialized Commission in Contraception, it was found that LARCs show superior efficacy and demonstrate pregnancy rates of less than 1% per year in perfect use. A key advantage of LARCs as compared to short-acting reversible contraceptives is their ability to maintain high efficacy irrespective of the user's compliance. Further they have considerably higher rates of satisfaction and continuity of use compared to short acting reversible contraceptives (10). NICE guidelines support this by stating that increasing the uptake of LARCs will significantly reduce the number of unintended pregnancies (11).

1.4 The role of BMI in abnormal uterine bleeding

Worldwide the prevalence of obesity has almost tripled in the last four decades, resulting in more women of reproductive age having an increased Body Mass Index (BMI) (12). Although data is limited on the effect of high BMI on contraceptives, there is some evidence that certain hormonal contraceptives including the transdermal patch and levonorgestrel (LNG) emergency contraception have decreased efficacy in women with higher BMI's. Recommendations are generally against the use of combined oral contraceptive (COC) use in overweight and higher BMI category women, given that a BMI ≥ 30 and use of COCs are both risk factors for venous thromboembolism(13). In light of this, it is necessary to consider BMI when selecting an appropriate contraceptive method for a patient. A recent ACOG (American College of obstetrics and gynaecology) Committee Opinion statement recommended that IUDs be considered as first-line choices for adolescents and highlighted the safety and efficacy of IUDs (13). Various studies have illustrated the high rates of menstrual cycle disturbance in high BMI patients (BMI's from 25 - 40 or greater), largely owing to the variations in gonadal steroid hormones concentrations attributed to obesity causing disruption of normal ovulation and dysfunctional uterine bleeding (13). This study aims to further evaluate the effect of BMI on bleeding patterns between in the two different LARC groups and in the DMPA-IM group.

1.5 Smoking and Abnormal Uterine Bleeding

Cigarette smoking has been shown to have a negative impact on reproductive health of females by accelerating onset of menopause, decreasing fertility and increasing the failure rate of oral contraceptives(14). On average smokers are 47 percent more likely to experience abnormal uterine bleeding than non-smokers (15) .

Cigarette smoking is associated with anti-estrogenic effects and may lower oestrogen levels (16). It has been found that premenopausal smokers have lower urinary levels of estrone, estradiol and estriol. Postmenopausal smokers have half the serum oestrogen of non-smokers and women who smoke are more likely to use hormone replacement therapy (HRT), with higher number of cigarettes smoked increasing this likelihood (14). The cause of abnormal uterine bleeding in smokers is likely to be related to the effect of smoking and nicotine on the endometrium. Smoking inhibits the growth of new blood vessels, while nicotine promotes local angiogenesis. It is proposed that these changes in standard physiology interfere with the ordinary course of cell growth, angiogenesis and apoptosis within the endometrium. Disorganised cellular events produce zones of defective new tissue, resulting in uneven shedding of the endometrial lining and irregular bleeding (13).

1.6 Discontinuation of contraceptive usage

Studies on contraceptive discontinuation have shown users perception of, and experience with side effects, to be a strong influence in their decision to stop contraception despite still requiring it (17). The World Health Organization (WHO) found after reviewing several Demographic and Health Survey's (DHS) that method-related concern was the highest reason for discontinuation across all contraceptive methods(18). Other studies have shown anxiety and misconceptions about health consequences of unscheduled bleeding as well as side effects to play a leading role in contraceptive discontinuation (17).

According to the latest DHS (2016), the contraceptive prevalence rate in SA for sexually active reproductive age women (15–49 years) is 60% (19). This relatively high rate fronts difficulties with service delivery; equitable access, and consistent use specifically among young and rural groups of women (20).

A qualitative study performed in South Africa in 2019 found that numerous factors impact women's experiences related to contraceptive uptake, initiation and continuation, including knowledge gathered from social and community networks (20). Menstrual cycle changes

including intermenstrual bleeding and amenorrhoea were shown to be of great concern to women, and were regularly the reason for change of method, or discontinuation (20).

Further research is necessary to understand the barriers against LARC use, particularly hormonal implants and intrauterine devices since these are accessible yet underutilised amongst South African women.

Finally understanding how AUB may present in each LARC method and with use of the short acting contraceptive, DMPA-IM, as well as improved understanding on the role of patient specific characteristics, is essential.
This may aid health care providers to accurately counsel patients on what menstrual cycle changes to expect and in doing so promote shared decision making to ultimately improve contraceptive method uptake and continuation.

2. Aims and Objectives:

The aim of this study is to explore patterns of AUB I associated with various contraceptives, specifically the copper-IUD, the levonorgestrel (LNG) implant and DMPA-IM. In addition to determine the relationship of high BMI and smoking on AUB patterns within a cohort of women recruited in the Evidence for Contraceptive Options and HIV Outcomes (ECHO) trial.

Objectives

1) To characterise the differences in abnormal uterine bleeding patterns among the 3 contraceptive methods.
2) To evaluate the relationship between high BMI (ranging from 25- 40 or more) and iatrogenic abnormal uterine bleeding.
3) To evaluate the effect of cigarette smoking on abnormal uterine bleeding.
4) To explore the role of AUB in the discontinuation of contraceptive methods.

3.Methodology:

3.1 Introduction:

The study will use data collected from participants who were enrolled in the ECHO trial (ClinicalTrials.gov Identifier: NCT02550067), a multicenter, randomised, open-label trial on HIV seronegative women seeking effective contraception in various research sites. The study was conducted between December 2015 and September 2017 across 12 research

sites in eSwatini, Kenya, South Africa and Zambia. Sites were selected based on high HIV incidence and geographical distribution. included free-standing research centers, university-affiliated research centers, and clinical sites providing reproductive health services(21).
The aim of the ECHO study was to compare the incident of HIV acquisition across three different methods of contraception including the DMPA-IM, Copper IUD and LNG implant (21). During the course of the trial along with demographic information and information needed to meet the study objectives, multiple questionnaires related to contraceptive side effects, method discontinuation, menstrual cycle changes etc were completed by trial participants.

3.2 Site of the study:

(21)Data will be obtained through the Match Research Unit (MRU) of the Wits Health Consortium (Pty) Ltd in the Department of Obstetrics and Gynaecology at the University of the Witwatersrand. MRU will provide a laptop containing data from 9 different ECHO trial study sites based in SA. MRU is based in Kwa-Zulu Natal (KZN), SA and was involved in data collection for the ECHO trial SA based sites.

3.3 Demographics of the sample and study design

Inclusion criteria:

- All participants enrolled in the South African sites (9 sites) of the ECHO trial which met the trial criteria set out by the inclusion criteria of the ECHO consortium (see appendix G).
- Women who were not pregnant
- HIV-seronegative
- Aged 16–35 years
- Seeking effective contraception
- Did not have medical contra- indications
- Agreed to use the assigned method for 18 months
- Reported not to be currently using injectable, intrauterine or subcutaneous implant contraception in the last 6 months
- Sexually active.
- Agreed not to participate in studies of drugs or vaccines or any other clinical research while participating in the study

Exclusion Criteria:

- Any women who was excluded from the ECHO trial as they were found to have met the exclusion criteria set out by the trial (appendix G). This includes:
- Medical contraindications (category 3 or 4 as detailed in the WHO Medical eligibility criteria for contraceptive use, 5th edition, Geneva: WHO) to DMPA, LNG implant or copper IUD's.
- Has received DMPA IM or Norethisterone enathane IM in the last 6 months
- Has used an implant or an IUD in the last 6 months
- Is pregnant or intending to become pregnant in the next 18 months
- Has previously enrolled in the study
- Has any conditions (social or medical), which in the opinion of the investigator, would make study participation unsafe or complicate data interpretation.
- Any women whose side effects CRF was not completed
- Women from ECHO study sites outside South Africa.

Study design: Subanalysis of a multicenter, randomised open label trial; the ECHO trial

3.4 Data collection

This research will involve a secondary analysis of ECHO trial data by reviewing data collected from case report files (CRF's) used in the original study.

The data analysed will include only those relevant to meet the specific objectives of the study including enrolment (appendix D), demographics (appendix E), contraceptive side effects (appendix F), physical exam (appendix G) and randomised hold/discontinuation (appendix H).

The sample size will consist of 5759 participants which will include participants from the 9 SA based sites. See table below for breakdown of participant numbers from each site.

Table showing the number of participants assigned to each site (21)

		Randomised Group						
Country	**Site**	**DMPA-IM**	**%**	**Copper IUD**	**%**	**LNG implant**	**%**	**Total**
Eswatini	Manzini	167	33.3	167	33.3	168	33.5	502
Kenya	Kisumu	299	33.2	301	33.4	301	33.4	901
South Africa	Brits	136	33.4	134	32.9	137	33.7	407
South Africa	Cape Town	187	33.4	186	33.2	187	33.4	560
South Africa	Durban	287	33.3	286	33.2	288	33.4	861
South Africa	East London	205	33.3	205	33.3	205	33.3	615
South Africa	Edendale	205	33.6	204	33.4	202	33.1	611
South Africa	Johannesburg	230	33.0	235	33.7	232	33.3	697
South Africa	Klerksdorp	187	33.7	183	33.0	185	33.3	555
South Africa	Ladysmith	219	33.5	217	33.2	217	33.2	653
South Africa	Soshunguve	269	33.2	269	33.2	272	33.6	810
Zambia	Lusaka	218	33.1	220	33.4	220	33.4	658
Total		2609	33.3	2607	33.3	2614	33.4	7830

The relevant data will be recorded onto a data collection sheet, specific for each participant (appendix A). The combined data from the data collection sheet of each participant will be analysed later.

4.Data Analysis

Data analysis will involve the analysis of the data pertinent to meet the objectives outlined above, specifically the responses to the questions stated in the data collection sheet (appendix A).

For objective one data on contraceptive side effects will be analysed (appendix D). Paying specific attention to patterns of bleeding including regularity, frequency, duration and volume of blood loss. Data will be used to compare bleeding patterns across each contraceptive method. Percentages of the frequency of each symptom will be determined in each contraceptive group, and pie charts will be used to display the percentage frequency of each symptom in each respective contraceptive method.

In order to meet objective two; evaluation of the role of BMI on iatrogenic AUB; data pertaining to physical exam will be evaluated (appendix E). BMI's will need to be calculated and patients categorised. The participants who fall within a BMI category of 25 upwards will be considered high BMI. Sub-classifications will include overweight (BMI 25-29.9), Class 1 Obesity (BMI 30.0-34.9), Class 2 Obesity (BMI 35-39.9) and Class 3 Obesity (BMI above

40). In each BMI group AUB patterns and frequency of symptoms will be explored and displayed on an appropriate graph to depict the findings.

Objective three aims to evaluate the effect of cigarette smoking on AUB. Data containing demographics (appendix C) will be analysed to meet this. Data for participants who smoked any number of cigarettes from one upwards per day will be recorded. AUB bleeding patterns in each group will be determined and the incidence of symptoms in relation to amount of cigarettes smoked will be explored. The bleeding patterns will be compared to matched participants who were non-smokers and this will be displayed pictorially using bar graphs.

For objective four the role of AUB in discontinuation of contraceptives; randomised method discontinuation data will be evaluated (appendix F). Data including participants who permanently discontinued the contraceptive, will be evaluated and their reason/s for discontinuation, specifically reasons pertaining to bleeding abnormalities. Frequency of discontinuation of each method will be calculated and the most common reasons will be charted within each method.

Once data have been combined into a single excel spread sheet and segregated into three groups: DPMA-IM, Copper IUD and LNG Implant group, descriptive statistics will be used to determine mean, mode, median and frequency values.

To test for statistical significance between the variables Stata software will be utilised. This will allow for the generation of statistical visualisations, reporting and assist with manipulation of data obtained in order to meet study objectives.

5.Ethics

Local research ethics committees (RECs) for each of the study sites (appendix C), the FHI 360 Protection of Human Subjects Committee and the World Health Organisation approved the ECHO study (ClinicalTrials.gov, number NCT02550067).

All participants provided written informed consent, which included counselling on randomisation, each contraceptive method, and their rights as participants in the research. (appendix B)

An application to the University of Witwatersrand Human REC will be made to conduct this sub-analysis on the data obtained during the ECHO trial. Permission has been obtained from the Match Research group for use of data from the South African sites involved in the study (appendix H)

6. Timing

	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul
Literature review												
Preparing protocol												
Protocol assessment												
Ethics application												
Collection data												
Data analysis												
Write up- thesis												
Writing up -paper												

7. Funding

Funding for the ECHO Trial was provided by the combined support of the Bill & Melinda Gates Foundation, the American people through the United States Agency for International; the Swedish International Development Cooperation Agency, the South Africa Medical Research Council; and the United Nations Population Fund. Contraceptive supplies were donated by the Government of South Africa and US Agency for International Development (21).

Funding for data collection at the MatCH Research site (KZN) a single trip from Johannesburg to KZN in order to collect laptop containing data and any printing costs will be paid by the primary researcher.

An application for funding from the Wits Masters of Medicine fund as well as to the South African Association of Trainees in Obstetrics and Gynaecology (SAATOG) research fund will be made to aid with publication fee's.

	Category	Amount	Total
Protocol write up and literature review	Fixed	0	0
Travel Match research site	Travel	Return flight 2000 (x1)	R2000
Collect data and analyze	Fixed	0	0
Printing	Fixed	500	500
Report and publication	Publication	2730.50	2730.50
			R5230.50

8. Limitations

This is a secondary analysis so it may be limited by not having all relevant information available. Certain variables may not be recorded on the CRF's, which would necessitate for the exclusion of this data.

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Protocol Appendix A: Data Collection Sheet

Participant ID: ☐☐☐ ☐☐ ☐☐☐☐ ☐

Site *Study* *Participant* *Chk*

Enrollment

To which arm is the participant assigned? ☐ *Copper IUD.* ☐ *Implant* ☐ *DMPA*

Demographics:

Age: ☐☐

years

Ethnic group or tribe: ☐☐ *tribe code*

Number of cigarettes per day: ☐☐ *number* ☐ *none*

Contraceptive side effects:

Since the last visit how would the participant describe…

12) Her bleeding pattern: ☐ *regular* ☐ *spotting only* ☐ *irregular* ☐ *no bleeding*
(go to item 17)

13) Date of onset of last vaginal bleeding ☐☐ ☐☐ ☐☐

dd *MMM* *yy*

14) Frequency of her bleeding pattern ☐ *too frequent* ☐ *about right* ☐ *infrequent*

15) Duration of bleeding episodes. ☐ *too short* ☐ *about right* ☐ *too long*

16) Volume of blood loss ☐ *too little* ☐ *about right* ☐ *too much*

17) Since her last visit what was the participants overall opinion of her bleeding pattern? ☐ *acceptable.* ☐ *not acceptable*

Physical exam:

systolic *diastolic* *not done*

Height ☐☐☐ *cm* blood pressure ☐☐☐ / ☐☐ ☐

Weight ☐☐☐ . ☐ *kg* temperature ☐☐ . ☐ °C

Randomised method hold/discontinuation:

1) Date of randomised study contraception hold/discontinuation: ☐☐ *dd* ☐☐☐ *MMM* ☐☐ *yy/*

Study contraceptive held/discontinued ☐ IUD ☐ Implant ☐ DMPA

2) Reason for holding or discontinuing randomised study contraceptive: Participant initiated holds

☐ Participant declined due to adverse event

☐ Participant declines: does not require contraception at this time

☐ Participant declines, no side effects but wants a different contraceptive

☐ Participant declines: other reason **(describe in comments)**

3) At this visit did the participant initiate a new study contraceptive?

☐ Yes ☐ DMPA ☐ IUD ☐ Implant

☐ No: no study contraception provided

☐ No: initiated on or referred for non-study contraceptive

4) Randomised study contraceptive was:

☐ Resumed

☐ Permanently discontinued

☐ Not re-established at the end of study participation

5) Comments:

_____

_____

Protocol Appendix B: Participant Consent Form

MatCH Research
Maternal, Adolescent and Child Health Research
Department of Obstetrics and Gynaecology
Faculty of Health Sciences
University of the Witwatersrand

ECHO Participant Enrolment Informed Consent Form

*Each participant must receive, read and understand this document **before** any study-related procedure*

STUDY NUMBER: FHI 360 Study #523201

STUDY TITLE: Evidence for Contraceptive options and HIV Outcomes (ECHO): A Multi Center, Open-Label, Randomised Clinical Trial Comparing HIV Incidence and Contraceptive Benefits in Women using Depot Medroxyprogesterone Acetate (DMPA), Levonorgestrel (LNG) Implant, and Copper Intrauterine Devices (IUDs)

SHORT TITLE FOR THE STUDY: The Evidence for Contraceptive options and HIV Outcomes (ECHO) Trial

SPONSOR: FHI 360 - 359 Blackwell St, Ste 200, Durham, NC 27701 USA

PRINCIPAL INVESTIGATOR: Prof JA Smit

INSTITUTION: MatCH Research, University of the Witwatersrand,
Department of Obstetrics and Gynecology

DAY TIME AND AFTER HOURS TELEPHONE NUMBERS: 031 001 1941 and 082 926 5762

To the potential Participant: *This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home **an unsigned copy of this consent** form to think about or discuss with family or friends **before making your decision. Feel free to do so.***

DATE AND START TIME OF INFORMED CONSENT DISCUSSION:

DD	**MMM**	**YYYY**

:
Time

INTRODUCTION

Hello, my name is _____. I work for MatCH Research. We understand you want to use a contraceptive to prevent pregnancy. Based on the screening visit, you are eligible for enrolment. We would like to invite you to join the "Evidence for Contraceptive Options and HIV Outcomes (ECHO)" research study. The study will find out more about the benefits and risks of different contraceptive methods.

1. Before you decide to join, we will read this consent form together. This consent form may contain words you do not understand. Please stop me at any time to explain any difficult words or information. After we read and discuss this form, you may take home an unsigned copy of this consent form to think about the study more. You may also want to discuss the study with your partner, family or friends, before deciding.

2. This consent form explains the goal of the study, what will be done, the benefits, the risks and what may be uncomfortable. It also explains other services that you can get. You should understand what is involved before you decide to join this study. If you join, you have the right to stop the study at any time you choose. However, it is important that you take the time to think about the study now and only agree to join if you believe you can stay for the entire 18 months. If you and many others decide to leave the study early, it will compromise the quality of the study results and prevent us from getting an accurate answer to our research question about the risks and benefits of different contraceptive methods. Getting an accurate answer could provide important information that could help millions of women who use contraception, and so we are asking you to think about this carefully before you commit to enrolling in the study.

3. If you have any questions, please ask me or any of the study staff.

4. You should only agree to join if you understand and accept all the procedures and risks of the study.

5. You cannot take part in studies of drugs, vaccines or any other clinical research study while you are in this study. Taking part in more than one study at the same time may not be safe. If you are participating in another study, you may not be able to join this study and we may stop the enrolment process. To check if you are participating in another study, we will enter your identity number and fingerprints into a computer system that will identify participants in other studies. By signing the Informed Consent Form, you are giving us permission to do this.

6. For your safety, it is important that you are honest with study staff about all aspects of your health.

7. If you decide to join this study, we will ask you to sign this form to show that you understand and agree to take part.

GOAL OF THE STUDY

The main goal of the ECHO study is to see if the risk of getting HIV is different with different contraceptives. We will also examine if women get pregnant more and if women experience more side effects depending on which contraception they use. We will compare three contraceptives that are all registered products being used by women around the world. These products include:

- Depot Medroxyprogesterone Acetate (DMPA), also known as Depo Provera, an injection given in the buttocks or arm every 3 months
- Levonorgestrel (LNG) implant (Jadelle), which is inserted in the arm, and
- Copper intrauterine device (copper IUD), which is inserted vaginally into the womb.

Prof J Smit conducts this ECHO study at MatCH Research. FHI 360 in the United States (US) coordinates the research study.

We are doing this study because we do not know if use of Depo Provera, the implant, or the IUD has an effect on the risk of getting HIV. Little research has been done on the use of the implant and the IUD, and the risk of getting HIV. Some studies have found that women using Depo Provera are more likely to get HIV, but other studies have found that DMPA does not make women more likely to get HIV. All of these studies have weaknesses and few were designed to answer this question. The ECHO study is designed to help us understand if these contraceptive methods change a woman's risk of getting HIV.

The World Health Organization (WHO)—a global group that works to coordinate international health—reviewed the information available and concluded the contraceptives in this study can be safely used by all women. The WHO said that women using these hormonal contraceptives should also use condoms and other HIV preventive methods. One of the reasons we are conducting the ECHO study, is because more research is needed to understand if Depo Provera, the implant, or the IUD affect the risk of contracting HIV. The results of this study will help us inform women in the future about HIV, pregnancy and other risks and benefits of these contraceptives.

LENGTH OF THE STUDY AND NUMBER OF WOMEN

The study will last about three years. About 7,800 women from several Eastern and Southern African countries will be in the study. At each study site up to 1,000 women will take part. The women will be between 16 to 35 years old. Each woman will be in the study for 18 months or less (if the study or study site closes).

PROCEDURES

Today's visit will take about 3-4 hours. If you join this study, we will give you one of three contraceptive methods: DMPA (Depo Provera) injections, the LNG implant, or a copper IUD. You will not choose your method. We will also not choose your method. A computer will choose your method by chance (like flipping a coin or throwing a dice). You will have the same chance of getting any of the three methods.

- **DMPA (Depo Provera)** is a hormone injection that lasts for 3 months. You will have an injection every 3 months.
- **The LNG implant** is made of two small hormone rods; the rods are thinner than matchsticks. We will insert the rods under the skin of your arm. The implant can last for 5 years. If you want to stop using the implant, a medical professional can remove it.
- The **IUD** is a small plastic and copper device, which is placed in the womb during a pelvic exam. A medical professional can easily remove the IUD if you wish to stop using it. The IUD can last for 10 years.

Once a method is randomly chosen by the computer, you will use the same method for the whole time you are in the study—18 months or less if the study closes.

Enrolment Visit

Today we will:

- Check and update your contact information
- Ask questions about your sexual behaviour and use of contraceptives
- Talk about your risks of HIV or other sexually transmitted infections (STIs), and how to prevent them
- Offer you condoms for HIV protection during sex
- Talk about different contraceptives
- Ask questions about any signs of STIs you may have
- Do a urine pregnancy test
- Take a blood sample to test your blood for STIs and for storage (up to 24 mL/approximately 2 tablespoons)
- Find out what contraceptive we will give you (through the computer)
- Give you the contraceptive chosen by the computer. Only the computer can choose the contraceptive for you, and we will ask you to use the same contraceptive during the whole study

Follow-up visits

After Enrolment, we will ask you to come back to the clinic for follow-up visits at month 1, month 3 and every 3 months thereafter. Please contact us or come to the clinic before your scheduled visit if you have any problems or worries. At your 1-month visit we will discuss your experience with your contraceptive and if you have an IUD, we will do a pelvic exam to verify the presence of the IUD string. If you have an implant,

we will verify implant presence by physically checking your arm. This visit will take about 2-3 hours. At your other follow-up visits, we will:

- Check that you are not taking part in any other research study
- Check and update your contact information
- Ask questions about your sexual behaviour and use of contraceptives
- Talk about your risks of HIV or other STIs, and how to prevent them
- Offer you condoms for HIV protection during sex
- Talk to you about your contraceptive
- Ask questions about any side effects or symptoms you may have
- Ask questions to check if you are pregnant, and test your urine for pregnancy if needed
- Give you HIV pre and post-test counselling
- Take your blood sample (up to 4 mL/less than 1 tablespoon). The blood will be used to test for HIV.
  - At the 6 month visit and the final study visit, we will take another blood sample (up to 40 mL/approximately 3 tablespoons) to test your blood for STIs and for storage.
  - Samples collected during this study will be tested at the clinic or by study researchers outside of the clinic either in South Africa or another country. Before your samples leave the clinic, they will be assigned a code and your name will not be on them.
  - If you have an HIV positive test during the study, we will provide you with counseling. We will also take another blood sample (up to 35 mL/approximately 2 tablespoons) that will be used to confirm the initial positive test and to perform a CD4 count, a measure of your immune function, and to measure the amount of HIV in your blood. We will also ask you to return to the clinic in 1-2 weeks for your final results.
  - If your HIV positive test is confirmed, at every follow-up visit thereafter, we will take a blood sample (up to 35mL/approximately 2 tablespoons) that will be used to perform a CD4 count and to measure the amount of HIV in your blood. We will also continue to provide counseling at every follow-up visit and refer you to care and treatment services in the community.

At any time during study follow up, if you or the study staff think you may have any health problems, you may need to undergo a physical exam and may need to provide blood or other samples for testing.

At your final visit, we will also do a pelvic examination, collect a specimen to test for STIs and a specimen for storage (if you give storage authorization), and treat or refer you for any curable infection. This visit will take about 2-3 hours.

Please tell us if you have any illness, injury or side-effects during the study. Please tell study staff of any medicines (prescriptions, over-the-counter and herbal) you are taking. You should also tell us if you use alcohol or other substances. This will not affect your ability to stay in the study.

KNOWN RISKS OF THE STUDY CONTRACEPTIVE METHODS

- There is a small chance of becoming pregnant while using one of these contraceptives.
- WHO considers all the contraceptives in this study safe and effective to prevent pregnancy (99% effective when women follow the instructions from their medical provider exactly). Not all women follow the instructions exactly, which is called "typical" use. The IUD and implant are still 99% effective during typical use. DMPA (Depo Provera) effectiveness decreases if injections are not given in time. Depo Provera may be only ~95% effective.
- Participating in this study does not increase your chance of getting pregnant.
- You can become pregnant when you stop using any of the contraceptives in this study.
- Women who stop using DMPA wait 4 months longer on average to become pregnant than women who have used the other methods. Many women can become pregnant within one or two months after stopping the implant or the copper IUD.
- Serious complications due to using contraceptives are very rare (less than one in 100 women), and are less likely than the complications of pregnancy. We will give you proper treatment in the clinic or by referring you for treatment
- The study contraceptive does not protect you against, or cause, STIs including HIV. The best way to protect against HIV is to use a condom every time you have sex. We will provide you with free condoms. The staff can give you more information about how to avoid contracting HIV.
- There may be possible changes in the chance of HIV transmission to your male sexual partner if you acquire HIV in the future. We do not know how use of contraceptives affects the chance of transmitting HIV to a sex partner. You should always use condoms during sex, and condoms will be given to you at the clinic.
- All contraceptives can have side effects and these can be upsetting, however you may not experience any of them. Most of the time, the side effects are not serious. For some side effects, you may need treatment. We will do our best to address any side effect that you may experience and give you treatment at the clinic or by referring you for treatment.

Before we continue to discuss each of these three contraceptives, please feel free to ask me any questions you may have.

The risks and possible side effects of the three methods are as follows:

DMPA (Depo Provera)

- *Serious risk:* blood clots (less than one in 100 women)
- *Possible side effects:* changes in menstrual bleeding can include irregular, prolonged, spotting or heavy bleeding, and no bleeding. You could also have headaches, dizziness, abdominal discomfort, weight gain and vaginal discharge. Thinning of the bones will usually go back to normal when you stop the injections.
- *Risk at injection*: you may feel a pinch or burning where the injection is made.

LNG implant

- *Serious risks:* blood clots (less than one in 100 women) and ectopic pregnancy (pregnancy in your tubes; this risk is very rare -- less than one in 1000 women).
- *Possible side effects:* changes in menstrual bleeding including irregular, prolonged, spotting and heavy bleeding, absence of bleeding, headache, breast pain, dizziness, stomach or pelvic pain, nausea, itching or pain at the insertion site or skin discoloration, vaginal discharge or itching, changes in weight and very rarely the implant may fall out before the skin has completely healed.
- *Risk at insertion*: you may feel discomfort or experience bruising where the implant is inserted.

Copper IUD

- *Serious risks:* pelvic infection (very rare --less than one in 100 women). The IUD may pierce (small tear) the wall of your womb (very rare --less than one in 100 women). Ectopic pregnancy (pregnancy in your tubes with an IUD in place); this risk is very rare -- less than one in 1000 women. If you get pregnant with an IUD in place, an ultrasound will be done as soon as possible to find where the IUD and the pregnancy are.
- *Possible side effects*: initial pain when the IUD is put in the uterus, menstrual cramps, heavy menstrual bleeding, vaginal discharge or irritation. You may feel the strings in the vagina and rarely the IUD may come out of the uterus and a new one need to be put in.
- *Risk at insertion*: you may feel discomfort or initial pain when the IUD is put into the uterus.
- *Risk at removal:* you may have cramping and bleeding during and after removing the IUD.

Possible risks from other study procedures

- You may have some pain when we take your blood. You may also feel dizzy or faint, and/or develop a bruise, swelling, or infection where we insert the needle.
- You may become embarrassed, worried, or anxious when we ask personal questions or when you receive HIV counselling.
- You may feel angry or upset if you learn you are HIV positive or if you have any other infection passed by sex. We will refer you for care and treatment if you are infected with HIV. We will also give you free treatment for any curable infection that is passed by sex.

BENEFITS OF STUDY PARTICIPATION

We will provide you with free condoms and screen you for STIs and give you free treatment or referral for any that are curable. If we find other health problems, we will refer you to local service providers. Participating in this study may help others in the future by increasing knowledge on contraceptive methods.

YOUR RIGHTS AS A PARTICIPANT IN THIS STUDY

Taking part in this study is voluntary. If you decide to take part, you can stop at any time, without saying why. If you refuse to take part or withdraw from the study, you will still get the care you normally receive as a client at KwaZulu-Natal Department of Health clinics.

YOUR RIGHTS IF YOU DECIDE NOT TO PARTICIPATE IN THE STUDY

If you decide not to take part in this study you will still receive the best current care, from your usual doctor, this may or may not include the study contraceptive

DISCONTINUATION OF YOUR STUDY CONTRACEPTIVE METHOD

Once you have joined the study, it is important you let us know if you wish to stop using your study contraceptive. Your health is our priority. If you want the IUD or implant to be removed, we will remove it. If you choose to stop receiving DMPA (Depo Provera), please note that the contraceptive effect lasts for about 3 months after the last injection. Although you can make the decision to withdraw from the study or to discontinue your randomly allocated contraceptive method at any time, you should understand that, if you start and stop your allocated method, it will be difficult to answer the study question.

STOPPING THE STUDY

- The study team may ask you to stop taking part in the study if it is best for you. If your taking part in the study ends early, we may ask you to return for a last visit for your safety.
- We may also ask you to stop the study at any time, if you do not give accurate information, or do not follow study guidelines.

We will provide you with any information that becomes available during the study which may affect your choice to be in the study.

IF YOU BECOME PREGNANT

We will ask you to stay in the study, but we will stop your contraceptive. We will refer you to a local service provider for pregnancy care. You will be responsible for your pregnancy healthcare.

IF YOU BECOME HIV POSITIVE

If you become HIV positive during the study, we ask you to stay in the study. We will counsel and refer you to a local service provider with experience in HIV care. The study will not cover cost of HIV care, however you will be referred to your local clinic for standard of care.

EMERGENCY CARE AND HOSPITALIZATION

If you seek emergency care or if you are admitted to a hospital during the study, please tell your doctor that you are/were enrolled in this study and inform us as well.

FINANCIAL ARRANGEMENTS

You will not pay for study medication, study visits or procedures. The study will cover costs of direct medical care for complications related to the study. All reversible contraceptives have a small chance of pregnancy,

which is not considered a complication. We will not treat any disease or condition not associated with the study. We will refer you for the correct care and treatment.

REIMBURSEMENT FOR TRANSPORT AND TIME

We will give you the study contraceptive for free. We will give you R150.00 as reimbursement for the enrolment visit. We will give you R150.00 as reimbursement for your follow-up visits. The amount for reimbursement has been calculated by looking at the cost to you in terms of travel to the study clinic and meals, time you spent at the clinic, and inconvenience caused to you when taking part in the research. If the study staff ask you to come to the clinic for an additional visit, you will receive R100.00. If you come to the study clinic because you believe you have a medical problem and the study staff agree your concern is related to the study, you will receive R100.00.

ETHICAL APPROVAL OF THIS STUDY:

The ECHO study protocol has been submitted to the University of The Witwatersrand, Human Research Ethics Committee and written approval has been granted by the committee. The study has been structured in accordance with the Declaration of Helsinki (last updated October 2013) which guides doctors in biomedical research involving human subjects. A copy can be obtained from study staff if you wish to review it.

PROBLEMS OR QUESTIONS

If you have any questions about the research tests, who to contact at the study site, or if you have a research related injury or any other problems related to the research tests, please feel free to contact the MatCH Research staff by visiting the site or phoning on (031 001 1941) or after hours on (082 926 5762). If you feel that you require more information than the clinic staff are able to give you please contact one of the people listed below:

Prof JA Smit (Principal Investigator) Cellphone: 082 926 5762	Ms Busi Maphumulo (Project Manager) Tel: 031 001 1944 Cellphone: 083 730 4448

This study is conducted in accordance with the Department of Health Guidelines for the Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa (2006), and has received ethical approval from the University of the Witwatersrand. If you have questions about your rights as a research participant, or complaints about how you were treated or feel that the study has caused you harm, please contact:	
Prof. Peter Cleaton-Jones Chairperson for the Committee for Human Research Ethics Committee University of the Witwatersrand Tel: 011 717 2301	

If you have questions about this trial you should first discuss them with your doctor or the ethics committee (contact details as provided on this form). After you have consulted your doctor or the ethics committee and if they have not provided you with the answers to your satisfaction, you can write to the Medicines Control Council (MCC) South Africa at:

The Registrar
Medicines Control Council SA
Department of Health
Private Bag X828
Pretoria 0001
Fax: (012) 395 8032
E-mail: gouwsj@health.gov.za

ADDITIONAL INFORMATION

Prof JA Smit is your study health care contact person. If at any time, you feel that your contraceptive method is causing you problems, or you have questions or concerns, please contact Prof Smit at 031 001 1941 or come to the site.

If you want any information regarding your rights as a research participant, or have any complaints regarding the research study, you may contact Prof. Cleaton-Jones, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (HREC), which is an independent committee established to help protect the rights of research participants at (011) 7172301. For **research information** you can contact Prof JA Smit who is the Principal Investigator for this study at 031 001 1941.

INSURANCE AND ABPI STATEMENT

MatCH Research through trial insurance will provide compensation for reasonable medical expenses incurred as a result of study-related injury or illness, determined according to the guidelines laid down by the Association of the British Pharmaceutical Industry (ABPI Guidelines), and Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa.

Please notify the study staff immediately of any complications, side effects and/or injuries during the study and the nature of the expenses to be covered. If a research related injury occurs, you have not waived any of the legal rights which you otherwise would have as a participant in this study by signing this form. Further detailed information on the payment of medical treatment and compensation due to injury can be obtained

from me or other study staff. We have a copy of the ABPI Guidelines and the Insurance Certificate, should you wish to review them.

The insurance does not cover and the study sponsors will not pay for:

- Medical treatment of other injuries or illnesses
- Injury caused by non-observance of the protocol.

The staff working on this study is covered by the insurance as long as they:

- Comply with the applicable requirements of the study protocol
- Comply with the regulations of the Medicines Control Council and the University of the Witwatersrand, Human Research Ethics Committee (HREC)
- Ensure that the handling and administration of the study contraceptives is in accordance with instructions and guidelines provided in the protocol, subsequent amendments and related documents.

This insurance is not intended to be and is not a substitute for the study staff's personal malpractice insurance.

Please note that if you have a life insurance policy you should enquire whether your insurance company requires notification of your intention to participate in a clinical study. Information to date is that it should not affect any life insurance policy taken out. Nevertheless, you are strongly advised to clarify it with the company concerned.

CONFIDENTIALITY

Efforts will be made to keep your personal information confidential. However, it is not possible to guarantee confidentiality. Your personal information may be disclosed if required by law. The study staff will use your personal information, if needed, to verify that you are not taking part in any other research studies. This includes studies conducted by other researchers that study staff knows about. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by:
Study monitors, University of the Witwatersrand Human Research Ethics Committee (an Ethics Committee is a committee that watches over the safety and rights of research participants), study sponsors and/or representatives as well as study staff.

In giving consent to participate in this study you will be consenting for these people to review the study data. These records will be utilised by them only in connection with carrying out their obligations relating to this clinical study.

Any information uncovered regarding your test results or state of health as a result of your participation in this study will be held in strict confidence. You will be informed of any finding of importance to your health or continued participation in this study but this information will not be disclosed to any third party in addition to the ones mentioned above without your written permission. The only exception to this rule will be cases of communicable diseases where a legal duty of notification of the Department of Health exists. In this case, you will be informed of the site's intent to disclose such information to the authorised state agency.

The researchers will do everything they can to protect your privacy. A description of this clinical trial will be available on www.ClinicalTrials.gov , as required by U.S. law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

RESEARCH-RELATED INJURY

It is unlikely that you will be injured as a result of having the research tests. If you are injured as a result of research procedures, the MatCH Research will give you immediate necessary treatment for your research related injuries. You will not have to pay for this treatment. You will be told where you can get additional treatment for your injuries. You do not give up any legal rights by signing this consent form.

VOLUNTEER AGREEMENT FOR THE ECHO STUDY

I, the participant, confirm that:

- I have been told about the clinical study, what will be done, and the benefits and risks.
- I have received, read and understood the above written information about the clinical study.
- I understand that personal details (sex, age and health) will be used in a study report without revealing my name.
- I may, at any time, stop taking part in the study, without losing any rights.
- I have had enough chance to ask questions and (of my own free will) declare myself prepared to take part in the study.

NOTIFICATION OF PERSONAL DOCTOR:

Please indicate whether you would like us to inform your personal doctor about your participation in the study

☐ **Yes,** I want you to inform my personal doctor

☐ **No,** I do not want you to inform my personal doctor

☐ I do not have a personal doctor

Signature of volunteer:

Signature/mark or thumbprint		Date of signature	DD	MMM	YYYY
Print name		Time of signature	:		

Signature of witness (if applicable):

Signature		Date of signature	DD	MMM	YYYY
Print name		Time of signature	:		

Signature of study staff taking consent:

Signature		Date of signature	DD	MMM	YYYY
Print name		Time of signature	:		

VOLUNTEER AGREEMENT FOR OFF-SITE VISITS

The study team at this clinic may visit you at home or at another place for study purposes. The study staff will explain the details of these visits (like the conditions of the place, the type of visit and the time period) and the steps to keep your information private. Outside clinic visits may affect your privacy, even if the study staff are careful not to disclose the reason for the visits.

You need to give permission before we can visit you outside of the clinic. Please read carefully the following sentences. Mark one option. Your choice will not affect your taking part in this study. You can withdraw your consent for the off-site visits at any time by telling staff at this clinic.

Check the appropriate statement about participation for off-site visits:

☐ **Yes**, I agree to be visited at home or at another place for study purposes

☐ **No**, I do not agree to be visited at home or at another place for study purposes

Signature of volunteer:

Signature/mark or thumbprint		Date of signature	DD	MMM	YYYY
Print name		Time of signature	:		

Signature of witness (if applicable):

Signature		Date of signature	DD	MMM	YYYY
Print name		Time of signature	:		

Signature of study staff taking consent:

Signature		Date of signature	DD	MMM	YYYY
Print name		Time of signature	:		

Protocol Appendix C: ECHO Ethics approval

University
of the Witwatersrand,
Johannesburg

Human Research Ethics Committee: (Medical)
FWA Registered No IRB 00001223

SECRETARIAT: Suite 189, Private Bag x2600, Houghton 2041, South Africa Tel: +27-11-274 9200 Fax: +27-11-274 9281

Dr Thesla Palanee-Phillips

Wits Reproductive Health & HIV Institute
Hillbrow Health Precinct, Hugh Solomon Building
Esselen Street (Cnr Klein St)
Hillbrow
2001

Fax: 086 554 1093

FAXED & COURIERED

11 April 2017

Dear Dr Palanee-Phillips,

PROTOCOL: FHI 360 STUDY #523201 - A MULTI CENTER, OPEN-LABEL, RANDOMISED CLINICAL TRIAL COMPARING HIV INCIDENCE AND CONTRACEPTIVE BENEFITS IN WOMEN USING DEPOT MEDROXYPROGESTERONE ACETATE (DMPA), LEVONORGESTREL (LNG) IMPLANT, AND COPPER INTRAUTERINE DEVICES (IUDS). THE EVIDENCE FOR CONTRACEPTIVE OPTIONS AND HIV OUTCOMES (ECHO) TRIAL

ETHICS REFERENCE NO: 141112

RE : APPROVAL FOR ECHO PROTOCOL VERSION 5.0 DATED 03 MARCH 2017

We acknowledge receipt of your letter dated 15 March 2017 with the following documentation pertaining to the above-captioned trial.

Amendment Date:	03-Mar-2017	Amendment Version:	Version 5.0
Amendment Number:		Received Date:	15-Mar-2017

The following has been approved by the Wits Human Research Ethics Committee: (Medical):

- FHI 360 Study #523201 Protocol Version 5.0 dated 03 March 2017 (Tracked and Clean Version)

Noted:
The revisions to the ECHO protocol are in responses to changes made by the World Health Organization (WHO) to the Medical Eligibility Criteria (MEC) for Contraceptive Use regarding the use of progestin-only contraceptives by women at high-risk of HIV infection. WHO changed the MEC category for progestin-only injectables (DMPA and NET-En) from a category 1 ('a condition for which there is no restriction for the use of the contraceptive method') to a category 2 ('a condition where the advantages of using the method generally outweigh the theoretical or proven risks')

Ethics Approval Date: 11 April 2017

The University of the Witwatersrand, Human Research Ethics Committee Approval Granted for the above mentioned study is valid for five years. Where required by Sponsor to have approval on a more frequent basis it remains the responsibility of the Sponsor and Investigator to apply for continuing review and approval, or for the duration of the Trial.

1. THIS APPROVAL IS SUBJECT TO THE FOLLOWING PROVISOS:

* A copy of the MCC Approval and/or MCC Notification letter must be submitted to the Ethics Regulatory Office Secretariat before the study commences / or where an Amendment may be implemented (IF MCC APPROVAL / NOTIFICATION IS APPLICABLE). It remains the responsibility of the Principal Investigator and/or Sponsor to ensure that the relevant approvals are in place.

* The study is conducted according to the protocol submitted to the University of the Witwatersrand, Human Research Ethics Committee. Any amendments to the protocol must first be submitted to the Human Research Ethics Committee for approval.

* During the study, the University of the Witwatersrand, Human Research Ethics Committee is informed immediately of :

- Any Unexpected Serious Adverse Events or Unexpected Adverse Drug Reactions, which, in the Investigator and/or the Sponsor's opinion are suspected to be related to the study drug. (Refer to POL-IEC-001 and SOP-IEC-005, Item 3.4).
- Any data received during the trial which, may cast doubt on the validity of the continuation of the study .

* The University of the Witwatersrand, Human Research Ethics Committee is notified of any decision to discontinue the study and the reason stated.

* The Investigators authorised by this approval participate in this study. Additional Investigators shall be submitted to the University of the Witwatersrand, Human Research Ethics Committee for approval prior to their participation in the study.

* In the event of an authorised Investigator ceasing to participate in the study, the University of the Witwatersrand Human Research Ethics Committee must be informed and the reason for such cessation given.

2. PRINCIPLES OF INFORMED CONSENT:

* The University of the Witwatersrand, Human Research Ethics Committee requires that in all studies, the Principles of Informed Consent are adhered to. This applies to volunteers as well as patients.

3. PROGRESS REPORTS:

* The University of the Witwatersrand, Human Research Ethics Committee requests that the MCC Progress Reports be submitted twice a year either in March and September or six monthly from start of study to the HREC Secretariat Office - 011 274 9281 and a report of the final results, at the conclusion of the study. (IF APPLICABLE)

4. REIMBURSEMENT TO PATIENTS FOR TRANSPORT:

* The Human Research Ethics Committee: (Medical) is in agreement that reimbursement per visit is according to the Medicines Control Council of SA and that reimbursement should be appropriate according to the situation.

5. TRANSPORT AND STORAGE OF BLOOD AND TISSUE SAMPLES IN SOUTH AFRICA:

* If blood specimens are to be stored for future analysis and is planned that such analysis will be done outside Wits, then the blood must be stored at a facility in South Africa agreed with the relevant IRB, with release of sub-samples only once projects have been approved by the local Research Ethics Committee applicable to where the analysis will be done as well as by the Wits Human Research Ethics Committee: (Medical).

6. GENETIC TESTING

* The Human Research Ethics Committee: Medical; will not approve open-ended genetic testing as this does not fit the Human Research Ethics Committee criteria.

7. GOOD CLINICAL PRACTICE

The South African Department of Health, Medicines Control Council requires Good Clinical Practice (GCP) Training for all Investigators in Clinical Trials, and that GCP training be renewed every three (3) years.

As yet, there are no National Guidelines for the content of GCP courses. Until these are available the Wits Human Research Ethics Committee (Medical) will note courses completed by Investigators without approval of the content of the individual courses.

8. THE SUPPORTING APPROVAL DOCUMENTS ARE ATTACHED:

8.1 Ethics Approval Form signed by the Chairperson of the HREC - Kindly return the copy of the Approval Form signed by the Principal Investigator /(s) per fax: 011 274 9281 for our records (this is only applicable with the initial Approval).

The above has been noted for the Ethics Committee information and records.

KINDLY FORWARD TO THE RELEVANT INVESTIGATORS / CRA / STUDY CO-ORDINATORS

Regards,

PROF PETER CLEATON-JONES

For and on behalf of the Human Research Ethics Committee: (Medical)

Protocol Appendix D: Permission for use of database

WITS MRU
MATERNAL, ADOLESCENT AND CHILD HEALTH RESEARCH UNIT
UNIVERSITY OF THE WITWATERSRAND

31 October 2022

Dr Natasha Di Rago
Dept of O&G
University of the Witwatersrand

Dear Dr Di Rago

I am writing to confirm the availability of the data for your MMED projects: Investigating the patterns of abnormal uterine bleeding in women using intramuscular depot medroxyprogesterone acetate, a copper intra-uterine device or a levonorgestrel implant for contraception.

The ECHO Management Committee has given permission for you to access to the data for your MMED project from "The Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial" for all nine South African sites.

We look forward to working with you on your analysis.

Regards,

M. Beksinska

Prof Mags Beksinska PhD
Deputy Executive Director
Wits MRU
Tel: 031 001 1941 / E-mail: mbeksinska@mru.ac.za

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South Africa
Tel: +27 0(31) 001 1900

Tel: +27 0(31) 001 1900

Protocol Appendix E: ECHO Enrolment

Enrollment (ENR)

SAMPLE: DO NOT FAX TO DATAFAX

ECHO TRIAL (DF/Net) 090

(ENR) 070

Enrollment ☐☐.☐

Participant ID: ☐☐☐ – ☐☐ – ☐☐☐☐ – ☐ (Site – Study – Participant – Chk)

Visit Date: ☐☐ dd ☐☐☐ MMM ☐☐ yy

Enrollment

1	Date the participant or guardian marked or signed the study ***screening*** consent form:	☐☐ dd ☐☐☐ MMM ☐☐ yy
	1a. Date the participant marked or signed the study ***screening*** assent form:	☐☐ dd ☐☐☐ MMM ☐☐ yy **OR** ☐ *N/A*
2	Date the participant or guardian marked or signed the study ***enrollment*** consent form:	☐☐ dd ☐☐☐ MMM ☐☐ yy
	2a. Date the participant marked or signed the study ***enrollment*** assent form:	☐☐ dd ☐☐☐ MMM ☐☐ yy **OR** ☐ *N/A*
	2b. Consented/assented for enrollment under protocol version #:	☐.☐
3	Did the participant agree to biological specimen and health data storage?	☐ *yes* ☐ *no* ☐ *pending*
4	Pregnancy test result:	☐ *negative* ☐ *positive* → ***Participant is ineligible.***
5	Date of first day of last menstrual period:	☐☐ dd ☐☐☐ MMM ☐☐ yy **OR** ☐ *unknown*
6	Date the participant was randomized:	☐☐ dd ☐☐☐ MMM ☐☐ yy
7	To which arm is the participant assigned?	☐ *DMPA* ☐ *Copper IUD* ☐ *Implant* → ***Complete IUD/Implant Insertion (INS) CRF.***
8	Did the participant receive the study contraceptive to which she was randomized on the date of randomization?	☐ *yes* ☐ *no* → ***If no complete item 8a, then specify reason in comments.***
	8a. Mark the reason participant did not receive her randomized study contraceptive:	☐ *Participant reason* ☐ *Clinician reason* ☐ *Other*
9	Comments: _____	

Version 1.0, 10-APR-15	**English**	**Completed by:** _____ *(initials/date)*

The **Enrollment (ENR)** CRF provides documentation of enrollment of eligible participants. Eligibility should be determined prior to completion of this form.

Item-specific Instructions:

Items 1 & 2	Making a mark in front of a witness who will sign the consent/assent form is considered "independent, written, informed consent/assent." If the participant is a minor, record the date the parent/guardian marked or signed the consent form. If the participant is not a minor, record the date the participant marked or signed the consent form.
Items 1a & 2a	If the participant is a minor, record the date the participant marked or signed the assent form. If the participant is not a minor and does not require parental/guardian consent, mark "N/A."
Item 2b	Record the protocol version to which the participant consented/assented. Do not record the consent form version number.
Item 3	Participants may consent to biological specimen storage at any point during follow-up. If the participant refuses biological specimen storage, mark "no." If the participant is undecided at enrollment, mark "pending" and update if the participant consents at a later visit.
Item 4	If the participant is pregnant, she is ineligible for enrollment. Stop all enrollment procedures and do not fax this form.
Item 5	For participants who do not remember the exact date of first day of bleeding of their last menstrual period, attempt to collect at least the month and year. If she does not know, prompt her with a calendar and record the best estimate. If day is unknown but month and year are known, line through the 'dd' box and write "unknown" or "UNK".
Item 7	If the participant was randomized to the IUD or Implant and received their contraceptive at the randomization visit, the **IUD** CRF must be completed.
Item 8	Mark "yes" only if the participant received her randomized study contraceptive on the same day that she was randomized.
Item 8a	If the participant did not receive her randomized study contraceptive on the same day that she was randomized, record the reason why she did not receive the randomized study contraceptive. For example: • If the participant declined to receive the contraceptive, mark "participant reason". • If the clinician determines that the participant cannot receive the randomized study contraceptive due to contraindication, mark "clinician reason". • If the insertion of her randomized study contraceptive was attempted but complications prevented complete insertion, mark "clinician reason".
Item 9	If item 8 is marked "no," describe a brief description of why the participant did not receive her randomized study contraceptive.

Protocol Appendix F: ECHO Demographics

SAMPLE: DO NOT FAX TO DATAFAX

ECHO TRIAL (DF/Net) 090 **(DEM) 090**

Participant ID: ☐☐☐ – ☐☐ – ☐☐☐☐ – ☐ (Site – Study – Participant – Chk) **Visit Date:** ☐☐ dd ☐☐☐ MMM ☐☐ yy

Demographics!

1	Date of birth:	☐☐ dd ☐☐☐ MMM ☐☐ yy **OR** Age: ☐☐ *years*
2	Current marital status:	☐ *never married* ☐ *married (monogamous)* ☐ *married (polygamous)* ☐ *separated* ☐ *divorced* ☐ *widowed*
3	Is the participant currently living with her husband/partner?	☐ *yes* ☐ *no* ☐ *n/a, no partner*
4	Highest level of education:	☐ *no schooling* ☐ *primary school, not complete* ☐ *primary school, complete* ☐ *secondary school, not complete* ☐ *secondary school, complete* ☐ *attended post-secondary school*
5	Ethnic group or tribe:	☐☐ *tribe code*
6	Number of alcohol drinks per week:	☐☐ *number of drinks* **OR** ☐ *none*
7	Number of cigarettes per day:	☐☐ *number of cigarettes* **OR** ☐ *none*
8	Does the participant own a mobile phone? **8a.** Does she have her phone with her?	☐ *yes* ☐ *no* → ***If no, go to item 9.*** ☐ *yes* ☐ *no*
9	How long did it take the participant to travel from home to the clinic today?	☐ *less than 30 minutes* ☐ *30-60 minutes* ☐ *1-2 hours* ☐ *greater than 2 hours*
10	Does the participant earn an income of her own? **10a.** How does she earn her income?	☐ *yes* ☐ *no* → ***If no, end of form.*** ☐ *formal employment* ☐ *self-employment* ☐ *other*

Version 1.0, 10-APR-15	**English**	**Completed by:** _____ *(initials/date)*

The **Demographics (DEM)** CRF collects information on all participants at the screening visit.

Item-specific Instructions:

<table>
<tr><td>Item 1</td><td>Do not fill in both date of birth and age. For participants who know their exact birth date, enter this information using the dd/MMM/yy format. For participants without an exact known date of birth, enter year of birth, if known, or approximate age if year of birth is not known.
For unknown date/month, line through the "dd" and "MMM" portion and write "unknown" or "UNK."</td></tr>
<tr><td>Item 2</td><td>Participants can be married by law, religious ceremony, or local or family custom.</td></tr>
<tr><td>Item 5</td><td>Record the 2 digit, country specific code that is associated with the participant's ethnic group or tribe.
<table>
<tr><th>South Africa</th><th>Swaziland</th><th>Zambia</th><th>Kenya</th></tr>
<tr><td>01 - Zulu
02 - Xhosa
03 - Indian
04 - Colored
05 - Other African Tribe
06 - White
99 - Other</td><td>07 - Swazi
99 - Other</td><td>08 - Bemba
09 - Nyanja
99 - Other</td><td>10 - Luo
99 - Other</td></tr>
</table></td></tr>
<tr><td>Item 6</td><td>Record the average number of alcoholic drinks the participant drinks per week. If the participant reports more frequent consumption than once per week but less frequent than twice per week, enter “01.” Anything else less frequent than once per week should be recorded as “00.” If the participant does not consume alcohol, mark “none.”</td></tr>
<tr><td>Item 7</td><td>Record the average number of cigarettes the participant smokes per week. If the participant reports smoking more than one cigarette per day but less than two per day, enter “01.” Anything else less frequent than one per day should be recorded as “00”. If the participant does not smoke cigarettes, mark “none.”</td></tr>
<tr><td>Item 8</td><td>If the participant has her own mobile phone, mark “yes”. If the participant shares a mobile phone, mark “no.”</td></tr>
<tr><td>Item 8a</td><td>If the staff see the phone, mark “yes.”</td></tr>
<tr><td>Item 9</td><td>Record the total time it took participant to travel to the clinic today. If the participant did not travel from home for this visit, ask her to estimate the travel time it will take her to get to the clinic.</td></tr>
</table>

Protocol Appendix G: ECHO Contraceptive Side Effects

Contraceptive Side Effects (CSE)

SAMPLE: DO NOT FAX TO DATAFAX

ECHO TRIAL (DF/Net) 090 (CSE) 150

Seroconverter ☐ Visit Month ☐☐.☐

CRF not administered ☐

Participant ID: ☐☐☐ – ☐☐ – ☐☐☐☐ – ☐ (*Site – Study – Participant – Chk*) **Visit Date:** ☐☐ *dd* ☐☐☐ *MMM* ☐☐ *yy*

Contraceptive Side Effects !

Has the participant had any of the following symptoms since her last visit?

				Ongoing?					Ongoing?
		Yes	*No*	*Yes*	*No*		*Yes*	*No*	*Yes*	*No*
1.	Headache	☐	☐	☐	☐	**7.** Breast pain	☐	☐	☐	☐
2.	Dizziness	☐	☐	☐	☐	**8.** Nausea	☐	☐	☐	☐
3.	Abdominal discomfort/ pain	☐	☐	☐	☐	**9.** Feeling like she has gained weight	☐	☐	☐	☐
4.	Menstrual cramps	☐	☐	☐	☐	**10.** Decrease in sexual desire	☐	☐	☐	☐
5.	Changes in vaginal discharge	☐	☐	☐	☐	**11.** Other, specify:	☐	☐	☐	☐
6.	Vaginal irritation/itching	☐	☐	☐	☐	_____				

Since the last visit how would the participant describe...

12. Her bleeding pattern: ☐ *regular* ☐ *spotting only* ☐ *irregular* ☐ *no bleeding* → ***Go to item 17.***

13. Date of onset of last vaginal bleeding: *dd* ☐☐ *MMM* ☐☐☐ *yy* ☐☐

14. Frequency of her bleeding pattern: ☐ *too frequent* ☐ *about right* ☐ *infrequent*

15. Duration of her bleeding episodes: ☐ *too short* ☐ *about right* ☐ *too long*

16. Volume of blood loss: ☐ *too little* ☐ *about right* ☐ *too much*

17. Since the last visit, what is the participant's overall opinion of her bleeding pattern? ☐ *acceptable* ☐ *not acceptable*

18. Since the last visit, has involvement in this study caused a social harm to the participant? ☐ *yes* ☐ *no* → ***If yes, complete Social Harm (SH) CRF.***

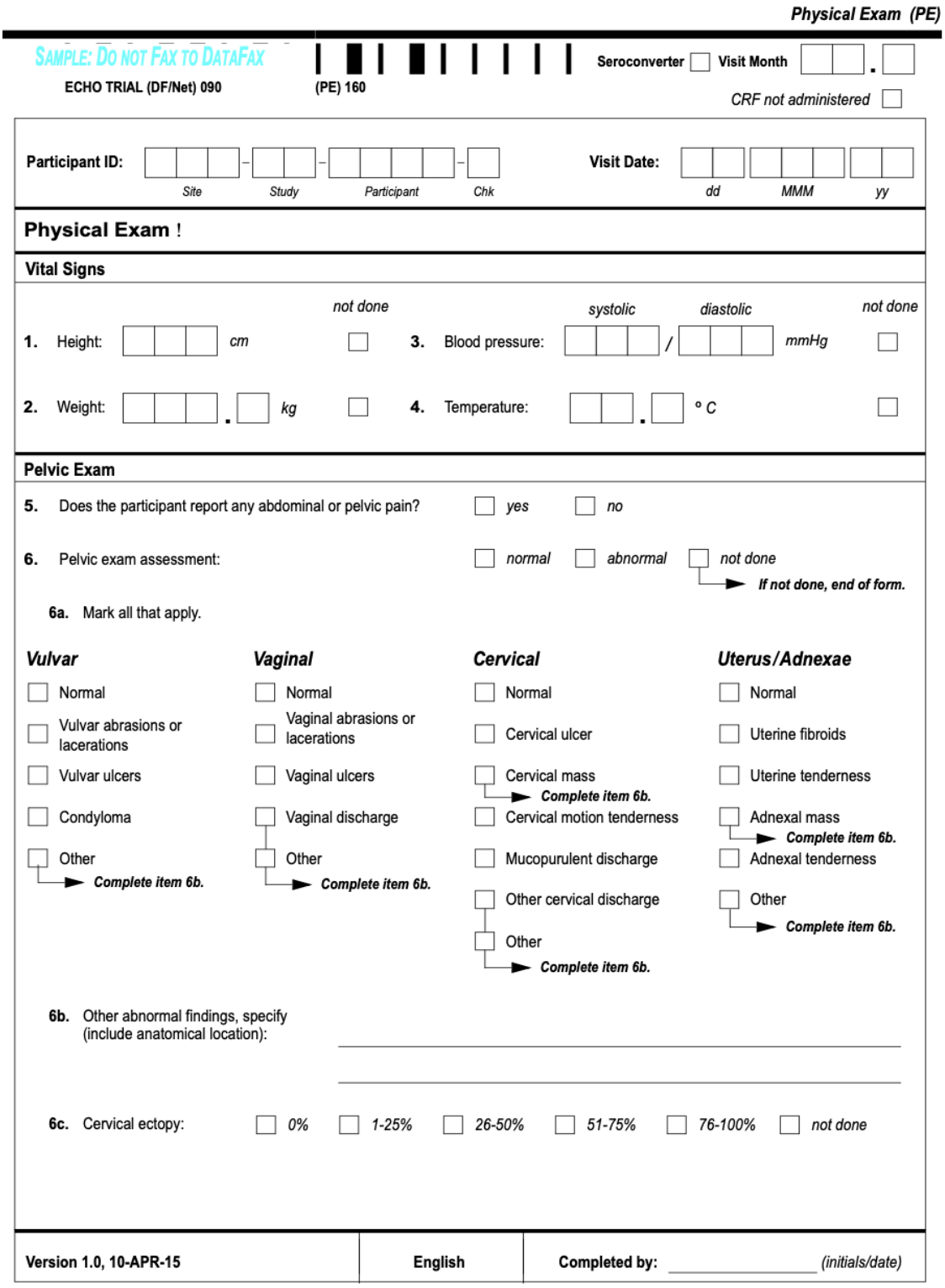
Version 1.0, 10-APR-15	**English**	**Completed by:** _____ *(initials/date)*

The **Contraception Side Effects (CSE)** CRF is used to record any side effects participants have experienced since the prior visit. This form should be administered at all scheduled follow-up visits or at any interim visit at which the participant reports side effects.

Item-specific Instructions:

CRF not administered box	If this form is not administered at a required visit, then it must still be faxed with the "CRF not administered" box marked.
Items 1-10	Mark 'yes' if the participant indicates she has experienced the symptom since her last visit. Record if the side effect is ongoing at the time of today's visit.
Item 11	Mark "no" if the participant reports no other symptoms since her last visit.
Items 12-17	Record based on conversations with the participant at today's visit.
Item 13	For participants who do not remember the exact date of first day of bleeding of their last menstrual period, attempt to collect at least the month and year. If she does not know, prompt her with a calendar, or history/event questions (e.g. Christmas), and record the best estimate. If day is unknown but month and year are known, line through the 'dd' box and write "unknown" or "UNK".
Item 18	This question should be asked in a culturally appropriate way in the context of a counseling session. Social harms may include: • Verbal abuse such as yelling, name calling or threatening; • Physical abuse such as hitting, slapping, or forcing someone to have sex against their wishes; • Economic abuse such as withholding money or taking money away. Only mark "yes" if the participant feels the social harm is related to her participation in the study. If "yes", fill out the **Social Harm (SH)** CRF.

Protocol Appendix H: ECHO Physical Exam



Physical Exam (PE)

SAMPLE: DO NOT FAX TO DATAFAX

ECHO TRIAL (DF/Net) 090

(PE) 160

Seroconverter ☐ Visit Month ☐☐.☐

CRF not administered ☐

Participant ID: ☐☐☐-☐☐-☐☐☐☐-☐ (Site – Study – Participant – Chk)

Visit Date: ☐☐ dd ☐☐☐ MMM ☐☐ yy

Physical Exam !

Vital Signs

		not done
1. Height: ☐☐☐ cm		☐
2. Weight: ☐☐☐.☐ kg		☐
3. Blood pressure: ☐☐☐ (systolic) / ☐☐☐ (diastolic) mmHg		☐
4. Temperature: ☐☐.☐ °C		☐

Pelvic Exam

5. Does the participant report any abdominal or pelvic pain? ☐ yes ☐ no

6. Pelvic exam assessment: ☐ normal ☐ abnormal ☐ not done → **If not done, end of form.**

6a. Mark all that apply.

Vulvar	*Vaginal*	*Cervical*	*Uterus/Adnexae*
☐ Normal	☐ Normal	☐ Normal	☐ Normal
☐ Vulvar abrasions or lacerations	☐ Vaginal abrasions or lacerations	☐ Cervical ulcer	☐ Uterine fibroids
☐ Vulvar ulcers	☐ Vaginal ulcers	☐ Cervical mass → **Complete item 6b.**	☐ Uterine tenderness
☐ Condyloma	☐ Vaginal discharge	☐ Cervical motion tenderness	☐ Adnexal mass → **Complete item 6b.**
☐ Other → **Complete item 6b.**	☐ Other → **Complete item 6b.**	☐ Mucopurulent discharge	☐ Adnexal tenderness
		☐ Other cervical discharge	☐ Other → **Complete item 6b.**
		☐ Other → **Complete item 6b.**	

6b. Other abnormal findings, specify (include anatomical location): _____

6c. Cervical ectopy: ☐ 0% ☐ 1-25% ☐ 26-50% ☐ 51-75% ☐ 76-100% ☐ not done

Version 1.0, 10-APR-15	English	Completed by: _____ (initials/date)

The **Physical Exam (PE)** CRF documents the physical and pelvic exam performed at the screening visit, final visit, possible seroconversion, and as clinically indicated. At screening, this form should only be faxed for participants who are enrolled.

Item-specific Instructions:

CRF not administered box	If this form is not administered at a required visit, then it must still be faxed with the "CRF not administered" box marked.
Item 6a	Mark the box for each abnormal finding observed. If the abnormal finding is not listed, mark "other" and describe the finding in item 6b.

Randomized Method Hold/Discontinuation (RMD)

SAMPLE: DO NOT FAX TO DATAFAX

ECHO TRIAL (DF/Net) 090 (RMD) 200

Seroconverter ☐ Visit Month ☐☐.☐

Participant ID: ☐☐☐ – ☐☐ – ☐☐☐☐ – ☐ (Site – Study – Participant – Chk)

Visit Date: ☐☐ dd ☐☐☐ MMM ☐☐ yy

Randomized Method Hold/Discontinuation!

1 Date of randomized study contraceptive hold/discontinuation: dd ☐☐ MMM ☐☐☐ yy → ***Study Contraceptive held/discontinued:*** ☐ *DMPA* ☐ *IUD* ☐ *implant*

2 Reason for holding or discontinuing randomized study contraceptive: *Mark all that apply.*

Clinician-initiated holds

		page #	page #
☐	SAE or AE → ***Complete Adverse Event (AE) Log:***	☐☐	☐☐
☐	Investigator discretion for safety concern other than SAE or AE → ***Describe in Comments, contact Safety Monitor.***		
☐	Pregnancy		
☐	Other reason → ***Describe in Comments.***		

Participant-initiated holds

		page #	page #
☐	Participant declined due to AE → ***Complete Adverse Event (AE) Log:***	☐☐	☐☐
☐	Participant declined: does not desire contraception at this time		
☐	Participant declined: no side effects but wants a different contraceptive		
☐	Participant declined: other reason → ***Describe in Comments.***		

3 At this visit, did the participant initiate a new study contraceptive?

- ☐ Yes → ***Indicate contraceptive:*** ☐ *DMPA* ☐ *IUD* ☐ *implant*
- ☐ No: No study contraceptive provided
- ☐ No: Initiated on or referred for non-study contraceptive

→ ***Complete Non-Randomized Contraceptive Tracking (NRCT) CRF.***

Item 4 may be completed at a later time than items 1-3. Fax this form again when the randomized study contraceptive is re-established, permanently discontinued, or when participant completes study follow-up without re-establishing study contraceptive.

4 Randomized study contraceptive was:

- ☐ Resumed → Date resumed: dd ☐☐ MMM ☐☐☐ yy ☐☐ At visit: **Seroconverter** ☐ ☐☐.☐
- ☐ Permanently discontinued
- ☐ Not re-established at end of study participation

5 Comments: _____

_____

Version 1.0, 10-APR-15	**English**	**Completed by:** _____ *(initials/date)*

The **Randomized Method Hold/Discontinuation (RMD)** CRF is used to document temporary or permanent contraceptive method holds. This form should only document holds or discontinuations of the participant's randomized study contraceptive. If the participant discontinues a non-randomized study contraceptive, this should be captured on the **Non-Randomized Contraceptive Tracking (NRCT)** CRF.

This CRF should be completed when a participant declines to continue her randomized study contraceptive, or when a clinical determination is made to discontinue the study contraceptive. An **RMD** CRF should be completed each time the randomized study contraceptive is discontinued. If a randomized study contraceptive is discontinued, resumed later, and then discontinued again, then a second **RMD** CRF should be completed at the time of the second discontinuation.

The **RMD** should not be completed:

- In cases of missed or late DMPA injections when then the contraceptive is otherwise being continued.
- When a participant has missed visits or is lost to follow-up.
- At study exit.
- If a participant has died.

Item-specific Instructions:

Item 1	Record the date of discontinuation/hold of the randomized study contraceptive. For women randomized to the implant or IUD, record the date of removal of the implant/IUD. For women randomized to DMPA, record the date that the participant declined or the clinician withheld the injection for which she is due.
Item 2	Indicate the reason(s) for holding or discontinuing the randomized study contraceptive. If more than one reason is present at the visit, multiple items may be marked. Only the initial reason(s) present at the visit when the discontinuation occurred should be listed. If additional reasons which contribute to not resuming the contraceptive occur at a later visit without the contraceptive having been resumed, these later reasons should not be listed as updates. If the discontinuation is due to an AE or SAE, the AE/SAE should be reported on an **Adverse Event (AE)** CRF and to the study safety monitor, and page number of the corresponding AE CRF recorded.
Item 3	Indicate whether the participant initiated a different study contraceptive (DMPA, IUD, or implant), no contraceptive, or if she initiated or was referred for a non-study contraceptive. All changes to contraceptive type should be recorded on the **RCT** & **NRCT** CRFs.
Item 4	This item may be left blank at the time of initial form completion, and must be completed and re-faxed if there is an update regarding the randomized contraceptive administration. If the randomized study contraceptive was resumed, indicate this with the date and visit code when the randomized study contraceptive was resumed. If a clinical determination was made that this participant should not use the contraceptive again due to clinical concerns, mark “permanently discontinued”, describe the reason in the comments section, and notify the study safety monitor. If the participant exits the study without having resumed her randomized study contraceptive, mark “not re-established at end of study participation.” If the contraceptive was not resumed, the date/visit code boxes should be left blank.
Item 5	If the reason for discontinuation was marked “other reason” or “participant declined-other reason,” the reason should be described in the comments section. Reasons for permanent discontinuation should also be noted in this section.

Protocol Appendix J: ECHO Inclusion and Exclusion

Table S1. Trial inclusion and exclusion criteria

Recruitment	Women were recruited from family planning/reproductive health clinics, clinics serving post-partum and post-abortion clients, other relevant clinics, and the general community.
Inclusion Criteria	To be eligible for the study a woman must have met all of the following criteria: • 16-35 years of age ○ Previously pregnant 16 and 17 year olds, where permissible by national regulations and local IRB approval • HIV-seronegative • Wants to use effective contraception • Is able and willing to provide written informed consent • Agrees to be randomised to either DMPA, LNG implant, or copper IUD • Agrees to use assigned method for 18 months • Agrees to follow all study requirements • Intends to stay in the study area for the next 18 months, and willing and able to provide adequate locator information • If has had a recent third trimester birth, is at least 6 weeks postpartum at time of enrolment • Is sexually active (has had vaginal sex within the last 3 months) or was pregnant within the last 3 months • Agrees not to participate in studies of drugs or vaccines or any other clinical research study while participating in this study.

Exclusion Criteria	A woman who reported or was found to have any of the following criteria was excluded from the study:
	• Medical contraindications (Category 3 or 4 criteria as detailed in the World Health Organization *Medical eligibility criteria for contraceptive use (*5th ed 2015, Geneva: WHO) to DMPA, LNG implant, or copper IUDs, including
	  ○ Persistent measured blood pressure 160/100 mmHg or higher, or history of uncontrolled hypertension due to vascular disease
	  ○ History of a stroke or heart attack
	  ○ History of rheumatic disease such as lupus, with positive or unknown antiphospholipid antibodies or low platelet count
	  ○ Multiple risk factors for cardiovascular disease including two or more of: a) smoked regularly for the past 6 months, b) history of hypertension, c) history of diabetes, and d) history of abnormal cholesterol/lipid disorder
	  ○ Diabetes for more than 20 years or diabetes with nephropathy, retinopathy, or neuropathy
	  ○ A current/acute blood clot in her legs or lungs
	  ○ History of severe liver cirrhosis or a liver tumor
	  ○ Current or previous breast cancer
	  ○ Endometrial, ovarian, or cervical cancer
	  ○ History of trophoblastic disease
	  ○ Unexplained vaginal bleeding between menstrual periods or bleeding after intercourse
	  ○ History of pelvic tuberculosis
	  ○ Known anatomical abnormality of the uterus incompatible with IUD insertion
	  ○ A recent septic abortion
	  ○ Untreated mucopurulent cervicitis on exam, untreated pelvic inflammatory disease (PID), or untreated known gonorrhoea or chlamydia
	• Has received a DMPA or NET-En injection in the last 6 months
	• Has used an implant or an IUD in the last 6 months
	• Is pregnant or intending to become pregnant in the next 18 months
	• Has had a hysterectomy or sterilization
	• Has previously enrolled in the study
	• Has any condition (social or medical), which in the opinion of the investigator, would make study participation unsafe or complicate data interpretation.

Appendix B: HREC Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Natasha Di Rago et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M230141 MED22-10-162

NAME: (Principal Investigator)	Dr Natasha Di Rago et al
DEPARTMENT:	Obstetrics and Gynaecology
PROJECT TITLE:	*Investigating the patterns of abnormal uterine bleeding in women using intramuscular depot medroxyprogesterone acetate, a copper intra-uterine device or levonorgestrel implant for contraception*
DATE CONSIDERED:	27/01/2023
DECISION:	Approved unconditionally
CONDITIONS:	This approval applies only to the study sites listed in Annex 1 attached. Further sites may be added on presentation of evidence of management approval to the HREC (Medical)
SUPERVISOR:	Dr Amy Wise
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	25/04/2023 **EXPIRY DATE:** 25/04/2028

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions.Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **January** and will therefore be due in the month of **January** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

25/04/2023

Date

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Annex 1

Protocol No. M230141 MED22-10-162 **Dr Natasha Di Rago et al**

Study sites approved under this Clearance Certificate

Study sites	Date of HREC (Med) Approval
1. Wits MRU Sites:	
a) Commercial City	25/04/2023
b) Edendale	25/04/2023

Dr CB Penny
Chair: Human Research Ethics Committee (Medical)
University of the Witwatersrand, Johannesburg

Date: 25/04/2023

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix C: Protocol Acceptance Letter

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

05 December 2022
Person No: 364575
PAG

Dr NC Di Rago
95 Pembroke Street
Sydenham
2192
South Africa

Dear Dr Natasha Di Rago

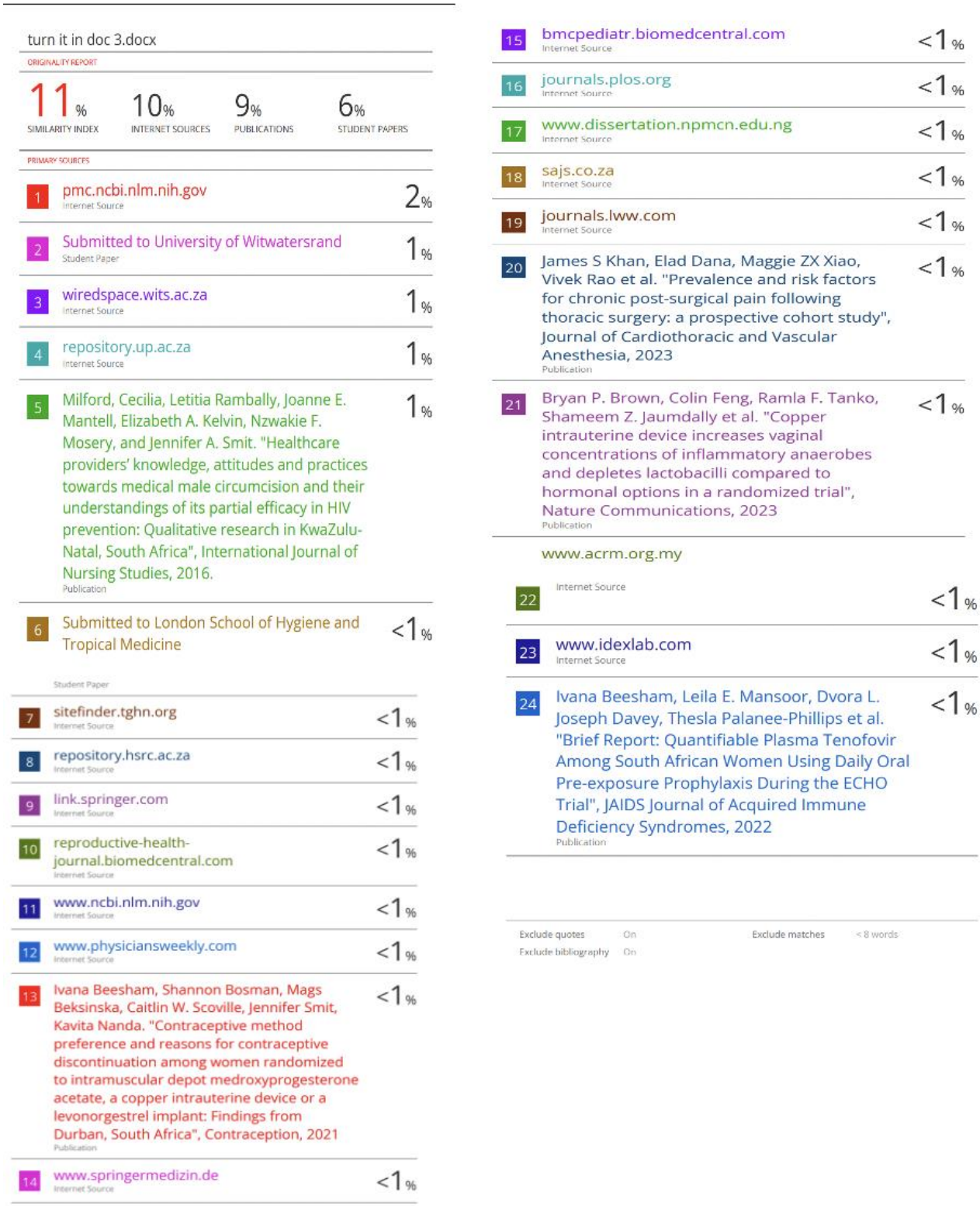
Master of Medicine in Obstetrics and Gynaecology: Approval of Title

We have pleasure in advising that your proposal entitled *Investigating the patterns of abnormal uterine bleeding in women using intramuscular depot medroxyprogesterone acetate, a copper intra-uterine device or a levonorgestrel implant for contraception* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix D: Plagiarism Report



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ORIGINALITY REPORT

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SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

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Appendix E: Plagiarism Declaration

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY:

I, Natasha Chiara Di Rago (Student number 364575), am a student registered for the degree of Master of Medicine (MMed) in the specialty of Obstetrics and Gynaecology in the academic year 2025.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or
- without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work
- except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: 

Date: 07 September 2025