

# BMJ Open Psychological, behavioural and physiological effects of three long-acting reversible contraception (LARC) methods: protocol for an ancillary study of the ECHO randomised trial

Mandisa Singata-Madliki,<sup>1</sup> G Justus Hofmeyr,<sup>1</sup>  
Florence Carayon-Lefebvre d'Hellencourt,<sup>2</sup> Theresa Anne Lawrie<sup>1,3</sup>

**To cite:** Singata-Madliki M, Hofmeyr GJ, Carayon-Lefebvre d'Hellencourt F, *et al.* Psychological, behavioural and physiological effects of three long-acting reversible contraception (LARC) methods: protocol for an ancillary study of the ECHO randomised trial. *BMJ Open* 2017;**7**:e019205. doi:10.1136/bmjopen-2017-019205

► Prepublication history for this paper is available online. To view please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2017-019205>).

Received 17 August 2017  
Revised 28 September 2017  
Accepted 26 October 2017



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<sup>1</sup>Effective Care Research Unit (ECRU), East London Hospital Complex, University of Fort Hare, East London, South Africa

<sup>2</sup>FHI 360, Durham, North Carolina, USA

<sup>3</sup>Cochrane Office, Education Centre, Royal United Hospital, Bath, UK

## Correspondence to

Dr Theresa Anne Lawrie;  
[tess@lawrie.com](mailto:tess@lawrie.com)

## ABSTRACT

**Introduction** This is the protocol for an ancillary study to the multicentre Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial, a three-arm randomised trial comparing the effects of depot medroxyprogesterone acetate (DMPA), the levonorgestrel (LNG) implant and the copper intrauterine device (IUD) on HIV incidence (NCT02550067 pre-results). The ancillary study will compare other non-contraceptive effects of these three long-acting, reversible contraceptions about which there is little existing comparative evidence.

**Methods and analysis** Women randomised to IUD, DMPA and LNG implant (1:1:1) at one of the ECHO trial sites will be asked to participate in the ancillary study at the 1-month follow-up visit. Research staff will interview women that consent to participate at the 3-month follow-up visit. Primary outcomes are depression, sexual dysfunction and menstrual disturbances. The Beck Depression Inventory will be used to assess depression and the Arizona Sexual Experiences Scale to assess sexual dysfunction. Participants will also be asked to prospectively complete a 28-day symptom diary. The required sample size is 522 participants. Depression scores will be analysed as continuous and categorical variables. Analysis will be by intention to treat.

**Ethics and dissemination** The ancillary study protocol received ethical approval from the University of the Witwatersrand Committee for Research on Human Subjects on 17 February 2016 (reference no. 14112). The results will be disseminated in a peer-reviewed open-access journal.

**Trial registration number** PACTR201706001651380.

## INTRODUCTION

There is a need to expand the choice of long-acting, reversible contraception (LARC) for women in low-income and middle-income countries (LMICs) where injectable progestogens, such as depot medroxyprogesterone acetate (DMPA), are often the only LARCs available. In such settings, findings from a Cochrane systematic review suggest that the

## Strengths and limitations of this study

- This ancillary study will compare the effects of three long-acting, reversible contraceptions (LARCs; intrauterine device, depot medroxyprogesterone acetate and levonorgestrel implant) on mood, sexual function, condom use and menstruation, for which there is very little existing evidence. The Evidence for Contraceptive Options and HIV Outcomes trial provides a unique opportunity to compare these non-contraceptive effects of LARCs within the context of a stringent randomised controlled trial protocol.
- While recall bias will be reduced by the use of the daily diary, results will still mostly be based on self-reported data.
- Non-contraceptive effects will be assessed at 3 months after participants are randomised to a LARC, and the lack of longer term follow-up might be a limitation.

copper intrauterine device (IUD) is probably more effective than DMPA at preventing pregnancy.<sup>1</sup> However, there remains a lack of robust evidence on non-contraceptive benefits, side effects and HIV risk of different LARC methods that is necessary to inform family planning health policies, contraceptive counselling and the individual woman's contraceptive choice.

Contraception is a complex intervention involving medical, physiological, psychological, behavioural and personal components to which both desirable and undesirable non-contraceptive effects have been attributed. LARCs include various non-hormonal (IUDs) and hormonal options (injections, implants, hormonal IUDs (eg, Mirena)), which quite plausibly have different side effects. Side effects attributed by women to their contraception method often lead

to contraception discontinuation, which is a common cause of unintended pregnancy. Therefore, providing women with accurate information about side effects of different contraception methods, and making a variety of methods available, could improve method adherence and effectiveness.

Limited evidence from two small randomised trials conducted among postnatal women in South Africa suggests that both postnatal depression and sexual dysfunction may be side effects of injectable progestogen use when administered soon after pregnancy.<sup>2,3</sup> These studies conducted by our South African research unit include a randomised double-blind, placebo controlled trial (RCT) of injectable norethisterone (NET-EN) versus placebo<sup>2</sup> and a single-blind randomised trial of DMPA versus the IUD.<sup>3</sup> Dysmenorrhoea and heavy periods were reported more frequently among women in the IUD arm of the latter study; however, this effect did not reach statistical significance. Another randomised trial conducted in our unit among women who had recently undergone termination of pregnancy found that more women in the injectable progestogen group had reduced libido and were more likely to use condoms than women in the IUD arm.<sup>4</sup> Reduced menstrual flow and amenorrhoea were effects seen more commonly in the injectable progestogen arms of the progestogen versus IUD studies,<sup>3,4</sup> whereas substantially more 'troublesome bleeding' occurred in the progestogen arm of the NET-EN versus placebo study in postnatal women.<sup>2</sup>

These and other non-contraceptive effects could influence HIV acquisition and disease progression among HIV-prevalent populations. While immune suppression and hypo-oestrogenic effects are thought to contribute to an increased risk of HIV acquisition among women using DMPA, it has been countered that this injectable method could also have protective effects for HIV acquisition due to associated amenorrhoea.<sup>5</sup> Reduced libido with injectable progestogens shown in two previous RCTs<sup>3,4</sup> might also mitigate the potential to increase HIV acquisition risk. Thus, the summary effect of psychological, behavioural and physiological mechanisms associated with effects of DMPA (and other LARCs) on HIV acquisition cannot be predicted without further research on non-contraceptive effects.

The large, multicentre 'Evidence for Contraceptive Options and HIV Outcomes (ECHO)<sup>i</sup> Trial' led by an FHI360/WHO consortium comparing HIV incidence and pregnancy rates of three different LARCs (IUD, DMPA, levonorgestrel (LNG) implant) provides a unique opportunity to also compare the effects of these LARCs on mood, sexual function and menstruation within the context of a stringent RCT protocol.

<sup>i</sup>The Evidence for Contraceptive options and HIV Outcomes (ECHO) Trial is a multicentre, open-label, randomised trial comparing HIV incidence and pregnancy rates in women randomised to depot medroxyprogesterone acetate (DMPA), the levonorgestrel (LNG) implant, and the copper intrauterine device (IUD).

## Objectives

This study aims to compare the effects of three LARCs (IUD, DMPA and LNG implant) on mood, sexual function, condom use and menstruation.

## METHODS

### Design and participants

This study is a randomised trial that will be conducted at the Effective Care Research Unit (ECRU) in East London, South Africa. It is ancillary to a large multicentre, open-label, randomised trial (The Evidence for Contraceptive Options and HIV Outcomes Trial (ECHO)) that has three parallel arms (1:1:1) comparing the effect of three LARCs (IUD, DMPA and LNG implant) on HIV incidence and pregnancy rates with a target sample size of 7800 women (ECHO trial registration: NCT02550067<sup>6</sup>; <http://echo-consortium.com/study-design/>).

Participant inclusion criteria are:

- ▶ 16–35 years of age;
- ▶ HIV seronegative;
- ▶ seeking effective contraception;
- ▶ able and willing to provide written informed consent;
- ▶ agrees to be randomised to either the copper IUD, DMPA or LNG implant;
- ▶ 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' post partum;
- ▶ is sexually active (has had vaginal sex within the last 3 months) or 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.

Women are not eligible to participate if they have medical contraindications to the copper IUD, DMPA or LNG implant (WHO Medical Eligibility Criteria category 3 or 4), if she has used the IUD, DMPA, NET-EN or LNG implant in the last 6 months, is pregnant or intending to become pregnant in the next 18 months, has had a hysterectomy or sterilisation, has previously enrolled in the study or has any condition (social or medical) which in the opinion of the investigator would make study participation unsafe or complicate data interpretation.

### Setting

The main ECHO trial is being conducted at 12 research sites in Kenya, South Africa, Swaziland and Zambia. This ancillary study will be conducted at one South African site only, ECRU, which recruits participants mainly from the community of Mdantsane, East London. South African settings have high HIV prevalence. In the 2012 South African National HIV Survey, the estimated HIV prevalence among black African women between the ages of 20 and 35 years was 31.6% (28.5%–34.9%).<sup>7</sup>

## Procedure

The ECHO trial's data management centre has prepared a computer-generated randomisation sequence using random block sizes between 15 and 30, stratified by site, to randomise 7800 women to one of three study arms (copper IUD, DMPA or LNG implant).<sup>6</sup> Participants are allocated to their contraceptive method centrally following online participant registration and, thereafter, research staff at the sites administers the allocated contraceptive method. Due to the nature of the interventions, participants and personnel are not blinded to group allocation. Follow-up visits for ECHO trial outcomes are performed at 1, 3, 6, 9, 12, 15 and 18 months.

For the purposes of the ancillary study, participating women at the ECRU site will additionally be asked to participate in a study on physiological, psychological and behavioural effects of LARCs at the first follow-up visit (3 months). If they agree, research staff independent of the main trial will obtain their informed consent for the ancillary study.

## Interventions

The three interventions compared in this study are

- ▶ copper IUD (Paragard-T 380A, Duramed)
- ▶ DMPA 150mg/mL (Depot-Provera, Pfizer) given intramuscularly every 12 weeks
- ▶ LNG subdermal implant 150mg (Jadelle, Bayer Schering Pharma).

## Outcomes and instruments

Primary outcomes of this ancillary study are sexual dysfunction, depression and menstrual disturbances (self-reported light, heavy or painful menstruation). At the 3 month follow-up visit for the ECHO study, women who consent to participate in the ancillary

study will be enrolled and interviewed by ancillary study researchers, which will administer a questionnaire. Depression and sexual dysfunction will be evaluated using the Beck Depression Inventory (BDI-II) and the Arizona sexual experiences scale (ASEX), respectively.<sup>8,9</sup> The BDI-II has been used in the same cultural context, translated into the local language (IsiXhosa) and previously validated in our study population.<sup>3,10</sup> We have used the ASEX scale in a previous study in our population and found it to be a useful tool,<sup>3</sup> although to our knowledge it has not been formally validated. In addition to assessment with these instruments, participating women will be asked to prospectively complete a 28-day daily diary at home of symptoms and behaviour, commencing on the day of their enrolment visit. A daily diary has been used in other studies that measure daily symptoms potentially related to the hormone fluctuations in women.<sup>11</sup> Parameters measured in the daily diary include sexual interest, activity and condom use, mood and characteristics of menstruation (table 1). To optimise compliance and the quality of self-reporting, research staff will show participants how to complete the daily diary by assisting them to complete their 'day 1' entries and will telephone or text message participants daily to remind them to complete the diary.

## Data collection and management

Participant data will be double entered on site from the data collection forms (questionnaire and daily diary) to a study database using EpiData Software (<http://www.epidata.dk>). Participant confidentiality will be protected by the following procedures: Participant data will be

**Table 1** Daily diary questions: please tell us what has happened from midday yesterday until midday today

	Question	Answer
1	Have you had menstruation?	0=none 1=light 2=normal 3=heavy
2	Have you had menstruation pain?	0=none 1=mild pain 2=severe pain
3	Have you had sexual intercourse?	0=no 1=yes with steady partner 2=yes with casual partner
4	If yes to question 3, was a condom used?	0=no 1=yes
5	Have you felt an urge to have sexual intercourse?	0=no 1=yes
6	Have you felt sad for no real reason?	0=none 1=mild 2=severe
7	Did you feel that your partner loves you?	0=no 1=yes 2=no partner

identified by a unique identification (ID) number not the participant's name, the study register will be kept separately from the data collection forms and will be kept securely in the research office, data will be entered by the unique ID number into the EpiData database which will only be accessible to research staff, study documents will be kept securely under lock and key for 5 years after completion of the study, and the study report will not contain names of participants. Details of trial monitoring and the composition of the data monitoring committee for the main ECHO trial can be found at <http://echo-consortium.com/study-design/>

### Statistical methods

Once the data have been checked, a statistician from the South African Medical Research Council will perform the statistical analysis using Stata Statistical Software V.12.<sup>12</sup> Analysis will be by intention to treat. Mean scores for the BDI-II and ASEX will be compared using mean differences with 95% CIs. In addition, we will use standard BDI-II thresholds to categorise any depression ( $\geq 14$ ) and major depression ( $\geq 29$ ).<sup>8</sup> Categorical outcomes will be compared using the  $\chi^2$  test unless events in any group are equal to or less than five, and then Fisher's exact two-tailed test will be used. Categorical data from the daily diary will be expressed as the proportion of positive responses (eg, if number of menstrual days is 7 days out of 28, the proportion will be  $7/28=0.25$ ); pooled data for each study group will then be expressed as mean values (of the individual proportions or means) with SD and compared using the t-test if the data are normally distributed. For non-parametric data, we will use the Wilcoxon test to compare medians and interquartile ranges. We will not impute missing data.

### Sample size

We based the sample size calculation on findings from a previous study in our population that reported the incidence of BDI-II depression scores  $\geq 14$  among women using injectable progestogens of 26.5%.<sup>3</sup> Assuming a 50% reduction in risk of depression with other LARC methods, we have calculated that we will need 158 women in each of the three arms ( $\alpha=0.05$ ,  $\beta=80\%$ ; EpiInfo). As randomisation is designed for the main ECHO trial and not the ancillary study, we plan to recruit an additional 10% to accommodate potential differences in group size due to block randomisation and in the event that a small proportion of women in the main trial decline participation in the ancillary study. Therefore, we will require a total sample size of 522 women (approximately 174 in each arm). We do not expect problems in recruiting this number of participants, given the large planned sample size of the main trial ( $n=7800$ ).

### Ethical considerations, approval and study registration

All participating women will be required to give written informed consent to participate in the ancillary study. Women found to have BDI-II scores of  $\geq 29$  during the study

interview will be referred to the relevant health professional at the participant's preferred healthcare centre.

The study was prospectively registered with the Pan African Clinical Trial Registry (PACTR) on 26 May 2016 (<http://www.pactr.org>) (PACTR201706001651380 pre-results). However, in June 2017, the principal investigator became aware of a problem with the registration (ie, that the study registration was incomplete) and corrected an error in the submission, at which point the registration became 'retrospective'. The original submission date is reflected in PACTR, which is a primary registry in the WHO Registry Network.

### Dissemination of findings

Once the study is completed, the listed authors of the protocol will write the ancillary study manuscript and plan to disseminate the findings by publishing the manuscript in an open-access journal.

### DISCUSSION

This ancillary study will provide unique data on any differences in physiological, psychological and behavioural parameters between the copper IUD, DMPA and LNG implant contraceptive options, because certain study findings will be based on daily symptom recording rather than symptom recall, which can suffer from recall bias.

A potential limitation of the study is the relatively short duration of follow-up (3 to 4 months), which is due to resource constraints. However, in an unpublished substudy of a study conducted in our research unit between 2008 and 2012 comparing the effects of the IUD with injectable contraception on pregnancy rates (with a median follow-up of 20 months),<sup>4</sup> we found that differences in mood were most marked at 3 months after randomisation. Therefore, we believe that our study with its 3–4 months' follow-up should capture important data.

Until recently, little attention has been paid to the impact of potential psychological, behavioural and physiological effects of LARCs on HIV acquisition. Evidence from this ancillary study on the non-contraceptive effects of LARCS may help to strengthen the scientific basis for the behavioural and physiological mechanisms potentially modulating HIV incidence that may be found by the main ECHO trial, which is due to report in 2019. The ECHO trial is a unique opportunity to investigate these potentially important effects.

**Acknowledgements** The Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial was made possible by the combined generous 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, the United Nations Population Fund, and the Government of South Africa.

**Contributors** MS-M conceived the study, contributed to study design and writing of the protocol. GJH contributed to study design and reviewed and advised on the draft protocol. FC-Ld'H contributed to study design and reviewed and advised on the draft protocol. TAL contributed to study design and writing of the protocol. All authors approved the final manuscript.

**Funding** The South African Medical Research Council (SAMRC) under the SAMRC Research Capacity Development Initiative (RCDI) Programme is funding this ancillary study.

**Disclaimer** Although a statistician at SAMRC will be assisting with data analysis and interpretation, SAMRC will play no role in the study design, collection of data, writing the report, the decision to submit for publication and has no authority over any of the research activities related to this study. The contents of this paper are solely the responsibility of the authors and do not necessarily reflect the views, decisions or policies of the institutions with which they are affiliated, the ECHO study funders, or the supporting governments.

**Competing interests** None declared.

**Ethics approval** University of the Witwatersrand Committee for Research on Human Subjects on the 17th February 2016 (Ethics reference no. 14112)

**Provenance and peer review** Not commissioned; externally peer reviewed.

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