The Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial

Helen Rees GCOB OBE MBBChir MA (Cantab) MRCGP DRCOG DCH

on behalf of the ECHO Consortium

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ECHO Team

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Starting point

Safe and effective contraception is essential to the health and development of women, children and families worldwide

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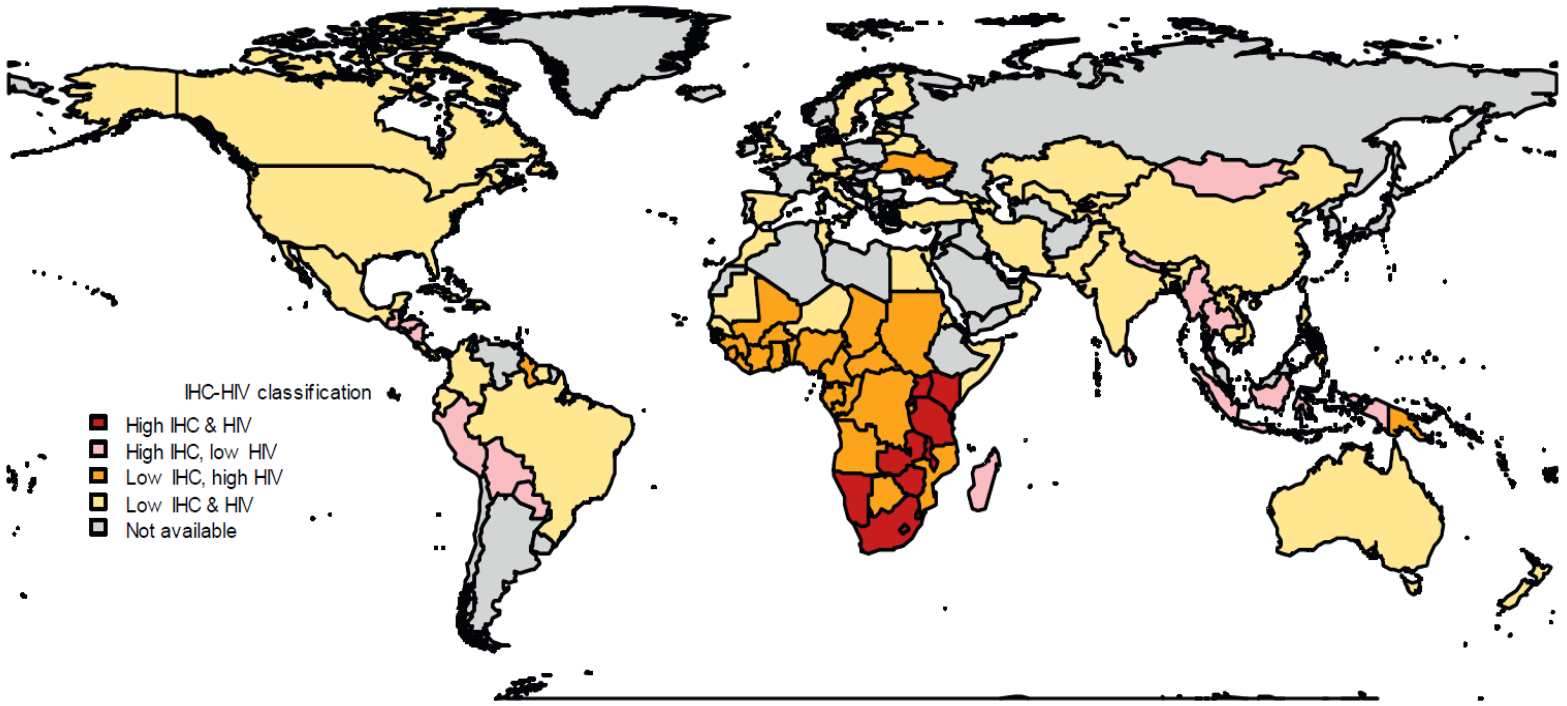
Overlap between injectable hormonal contraception use and HIV prevalence



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Only observational data have been available

- 25+ years of epidemiologic and biologic studies have tried to determine whether there is truly increased risk of HIV acquisition associated with use of hormonal contraception.

Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study

*Renee Heffron, Deborah Donnell, Helen Rees, Connie Celum, Nelly Mugo, Edwin Were, Guy de Bruyn, Edith Nakku-Joloba, Kenneth Ngure, James Kiarie, Robert W Coombs, Jared M Baeten, for the Partners in Prevention HSV/HIV Transmission Study Team**

Progesterone implants enhance SIV vaginal transmission and early virus load

Preston A. Marx[1,2], Alexander I. Spira[1,2], Agegnehu Gettie[1], Peter J. Dailey[3], Ronald S. Veazey[4], Andrew A. Lackner[4], C. James Mahoney[5], Christopher J. Miller[6], Lee E. Claypool[7], David D. Ho[1] & Nancy J. Alexander[8]

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Summary of evidence

- **Progestogen-only injectables** (particularly **DMPA-IM**)**:** linked to ↑ HIV risk
  - In one meta-analysis, the magnitude of effect was 1.40 (95% CI 1.23-1.59)
  - Importantly, we do not know whether DMPA use *causes* increased risk
  - **NET-EN:** less HIV risk than DMPA? (although limited data)
  - **DMPA-SC:** no data
- **Hormonal implants** & **hormonal/non-hormonal IUDs:** even less data

WHO Guidance, 2017


World Health Organization

Hormonal contraceptive eligibility for women at high risk of HIV

Guidance statement

Recommendations concerning the use of hormonal contraceptive methods by women at high risk of HIV

Executive summary

The World Health Organization (WHO) convened a technical consultation during 1–2 December 2016 to review new evidence on the risk of HIV acquisition with the use of hormonal contraception (1). The issue was recognized as a critical one, particularly for sub-Saharan Africa, where women have a high lifetime risk of acquiring HIV, hormonal contraceptives constitute a significant component of the contraceptive method mix and unintended pregnancy is a common threat to the well-being and lives of women and girls.

A wide range of stakeholders were present at this meeting, and serving on the Guideline

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Women can use progestogen-only injectables but should be advised about:

- Concerns about possible ↑ risk of HIV
- Uncertainty about causal relationship
- How to minimize their risk

The WHO guidance also called for data from randomised trials.

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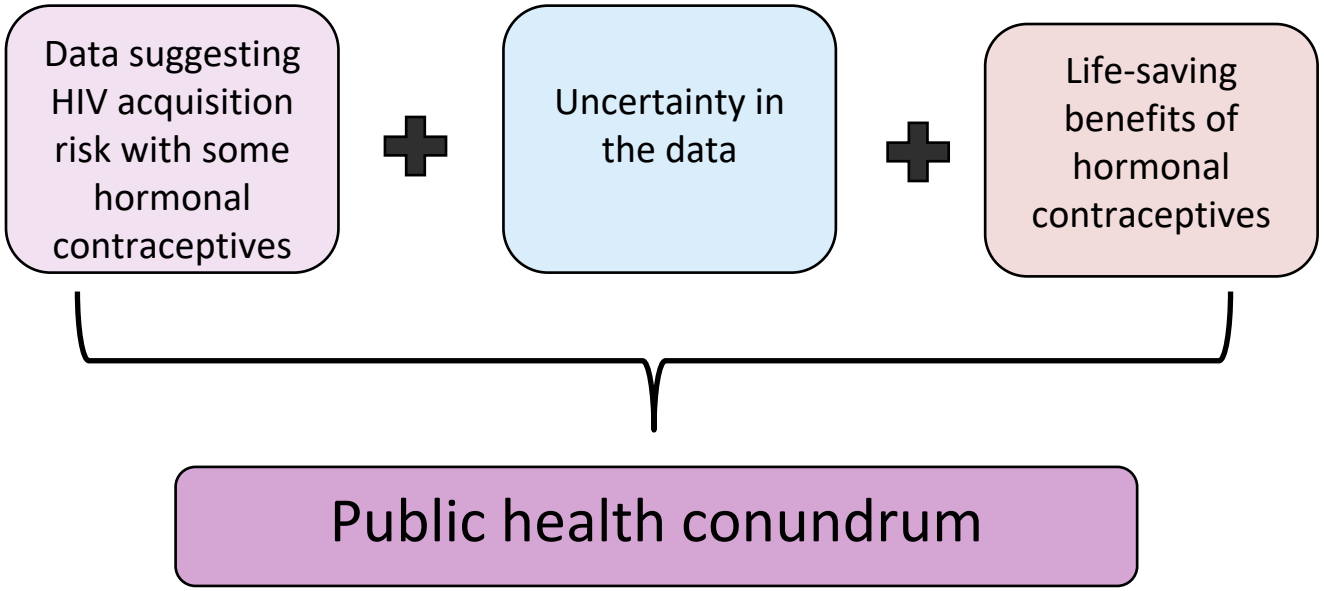
The challenge



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)

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ECHO study goal

To assess whether the **risk** of acquiring HIV differs with use of three different family planning methods, and how that risk balances against the **benefits** of those methods

DMPA-IM

LNG implant

Copper IUD

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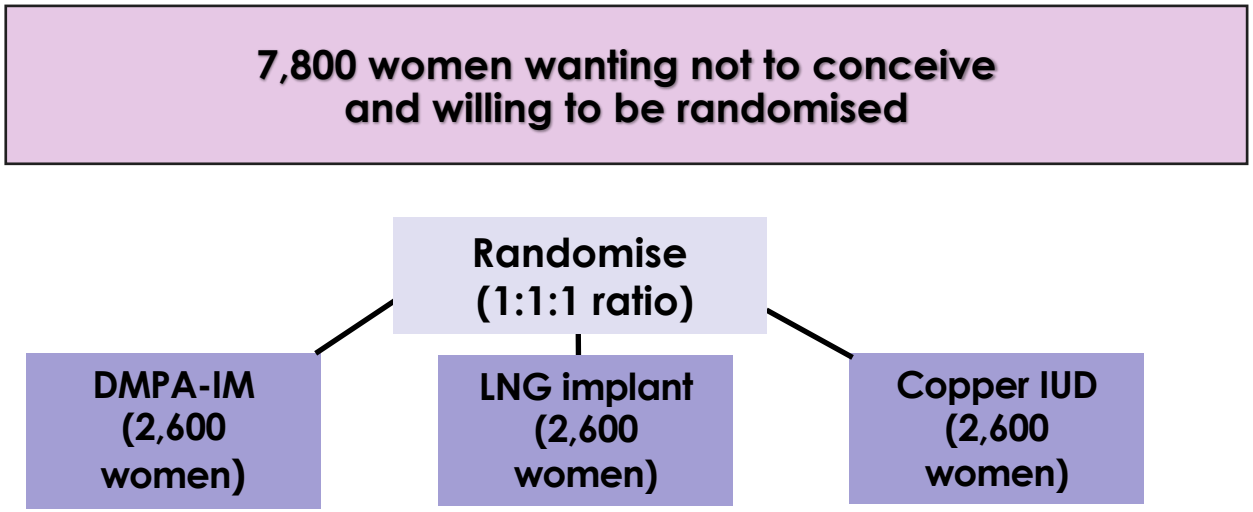
ECHO study design



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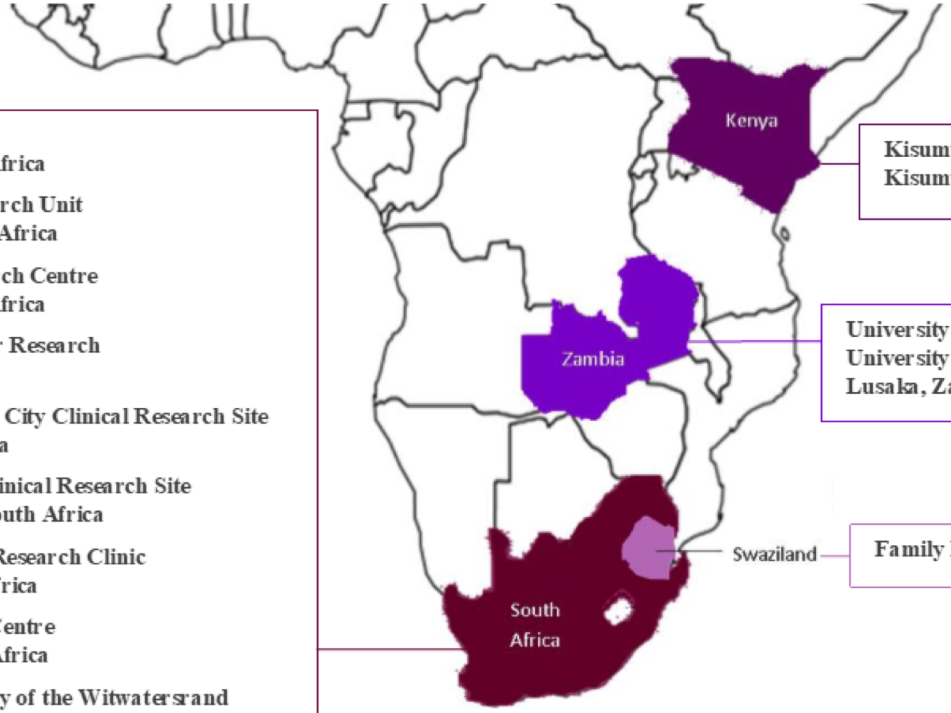
Study setting: 12 sites in 4 countries



Aurum Institute
Klerksdorp, South Africa

Effective Care Research Unit
East London, South Africa

Emavundleni Research Centre
Cape Town, South Africa

Madibeng Centre for Research
Brits, South Africa

MatCH Commercial City Clinical Research Site
Durban, South Africa

MatCH Edendale Clinical Research Site
Pietermaritzburg, South Africa

Qhakaza Mbokodo Research Clinic
Ladysmith, South Africa

Setshaba Research Centre
Soshanguve, South Africa

Wits RHI / University of the Witwatersrand
Johannesburg, South Africa

Kisumu East District Hospital Research Care & Training Program
Kisumu, Kenya

University of North Carolina's Division of Global Women's Health - University Teaching Hospital (UNC—UTH)
Lusaka, Zambia

Family Life Association of Swaziland—ICAP

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ECHO visits

- Study visits at one month, **then quarterly for up to 18 months:**
  - HIV testing and contraceptive counselling
- Women receive comprehensive **contraceptive and HIV prevention package:**
  - Counselling
  - Condoms
  - Offer of partner HIV testing
  - STI screening and treatment
  - Offer of oral PrEP (introduced during study as national policies allowed)

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ECHO oversight

- Ethics committees and qualified independent clinical monitors
- A safety oversight committee, available 24/7 for clinical advice
- Global Community Advisory Group and Community Advisory Boards (CAB) at each site
- Good Participatory Practice plans for each site
- An independent Data and Safety Monitoring Board

Local CAB meeting

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ECHO progress

7,830

Women enrolled

100%

Enrolment target reached and follow-up visits completed as of 31 October 2018

Mid–2019

Study results expected

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We do not yet know the results, but…

ECHO summary

Design	Multi-center, open-label randomized trial, with random allocation to: DMPA-IM, LNG implant, or copper IUD
Population	Sexually active HIV-uninfected women, ages 16-35 years seeking highly effective contraception, willing & *voluntarily consented* to be randomly-assigned to any of the three study methods
Sample size	7,800 women (~2,600 per study group)
Outcomes	Primary = HIV (**80% power to observe 50%** increase, comparing each method to each of the other two methods) Secondary = pregnancy, safety, method continuation
Duration	Up to 18 months per woman

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Why a randomized study?

- Only a randomized clinical trial can evaluate for evidence of causal relationship – i.e., that using a particular contraceptive method leads to increased risk of HIV

- A randomized trial will provide the highest-quality evidence to:
  - Enable women to make fully informed choices
  - Inform clear counselling messages for clinicians
  - Offer guidance for policymakers and programs

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ECHO and the WHO's MEC classifications

- For women at high risk of HIV, the WHO 2017 MEC classifies:
  - DMPA-IM = 2
  - LNG implant = 1
  - Copper IUD = 2 (for women at high risk for STI, including HIV)

Classification of Known Conditions	Definition
1	No restriction on use
2	Benefits generally outweigh risks
3	Risks generally outweigh benefits
4	Unacceptable health risk

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ECHO: What can the study tell us?

- **HIV incidence:** comparison of how many women became HIV infected in each group

  DMPA-IM vs. IUD | Implant vs. IUD | DMPA-IM vs. Implant

- Studies of **possible biologic mechanisms** (ancillary studies to ECHO)
- Direct comparison of **how many women decided to stop using the contraceptive method** they were assigned during & at the end of the study
- Comparison of **how many women became pregnant** in each contraceptive group

ECHO: What it cannot tell us

- HIV risk
  - Compared to **no contraception** (because we did not have a control group of women not using contraception)
  - For **methods not tested** (e.g., COCs, NET-EN, DMPA-SC, ETG implant, progestin IUS, etc.)
- Differences in HIV risk between methods **smaller than an approximately 35% increase**

Importantly: *ECHO will provide evidence — not prescriptions — for policy, program, and individual decision-making*

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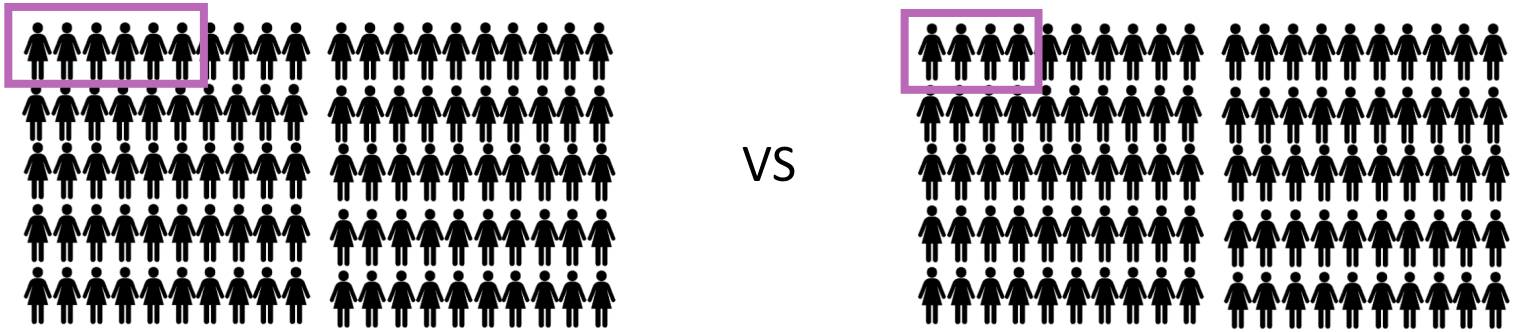
What does a 50% increased risk mean?

- Prior to starting ECHO, the trial estimated that approximately 4 out of 100 women in the study would acquire HIV each year. A 50% increased risk for one of the methods would mean 6 out of 100 instead of 4.



The HIV incidence estimate of ~4% per year for ECHO was based on rates of new HIV infections in women in prior HIV prevention trials that took place in similar geographic areas to ECHO (all of which included condoms, risk-reduction counseling, STI treatment, like ECHO).

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Thinking through some possible ECHO outcomes

- **No difference in HIV risk**, with similar HIV incidence for the three groups (DMPA-IM = LNG implant = copper IUD)

Thinking through some possible ECHO outcomes

- **Difference in HIV risk**, with DMPA-IM ≥1.5-fold greater HIV incidence than the LNG implant and/or copper IUD
  - → The ECHO trial is designed with high statistical power to detect at least a 50% increase in HIV risk
  - → The observational data suggest DMPA-IM could have a ~40-50%, or greater, increased HIV risk

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Thinking through some possible ECHO outcomes

- **Difference in HIV risk**, with highest HIV incidence for the copper IUD or LNG implant

  → While this might be a surprising result, remember that there are currently very few data to assess HIV risk for implants and IUDs.

  → ECHO is designed to have statistical power to detect at least a 50% increased HIV risk for any of the methods, compared to each of the other two methods.

What's next

- Data analysis is ongoing
- Results dissemination estimated in mid-2019
- Results presented to WHO Guidance Steering Group, who will consider new data and whether there is need for policy change

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What ECHO will contribute

- The highest quality scientific evidence on the question of hormonal contraception and HIV risk

- Needed information for women, so they can make informed choices about contraception and HIV prevention

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African Civil Society Dialogues, 2018

- Take action, no matter what the trial finds
  - More funding for family planning products and transporting them to where they are needed so that choices are on the shelves in public and private clinics
  - More training for providers and policy makers on this issue and more effort to make SRHR and HIV services to work together, share clinics and resources In the introduction of oral PrEP, Sayana Press (DMPA-SC) and other new strategies (e.g. dapivirine ring), all materials, education and outreach should make women, choice and human rights the central themes

Source: AVAC

ECHO Funders

BILL & MELINDA GATES foundation

PEPFAR

USAID
FROM THE AMERICAN PEOPLE

Sida

saMRC
advancinglife

UNFPA

Republic of South Africa

Contraceptive supplies donated by USAID and the Republic of South Africa

The ECHO Trial is dedicated to Ward Cates

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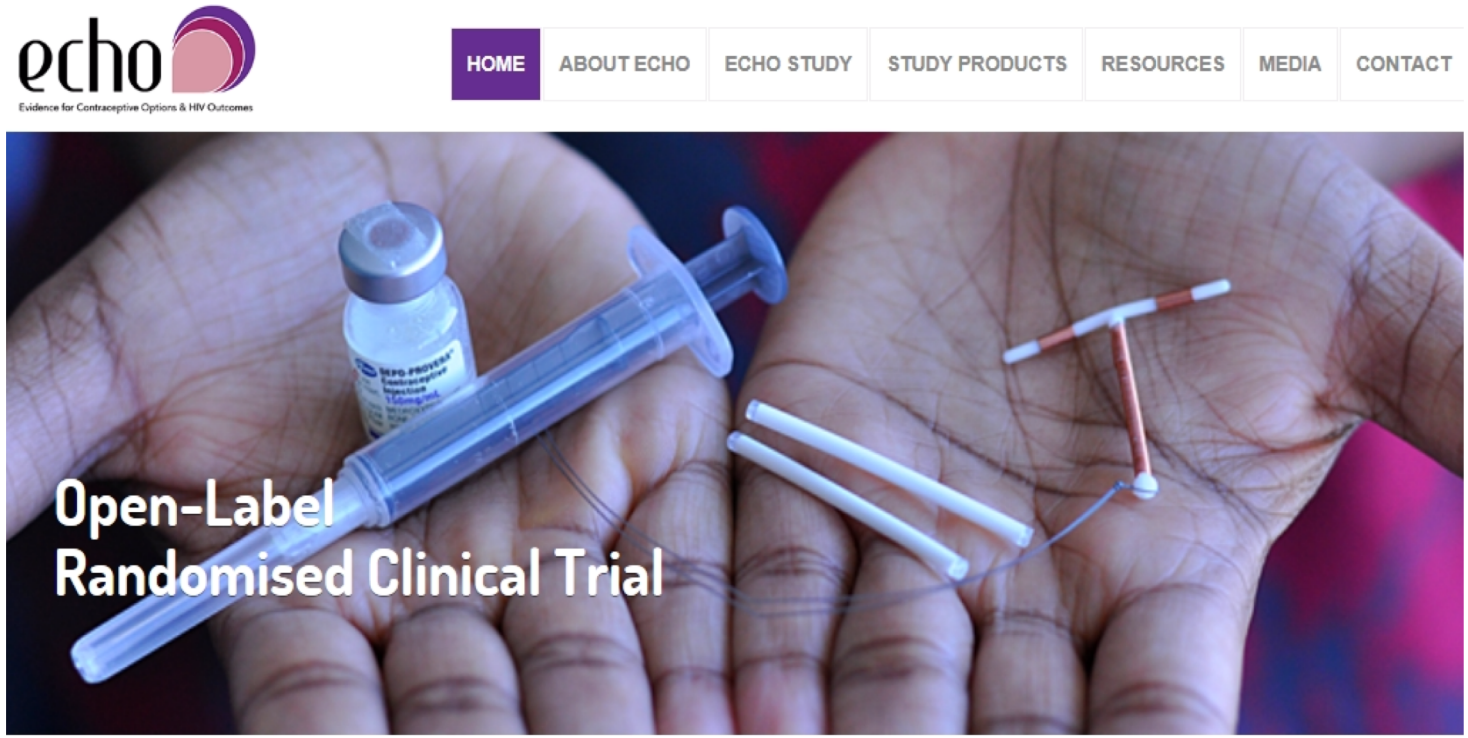
Website - www.echo-consortium.com



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