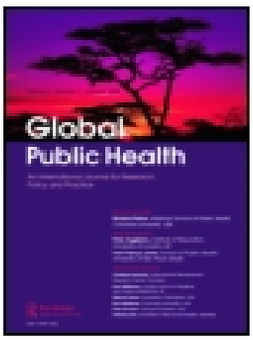

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In the name of science: Ethical violations in the ECHO randomised trial

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ABSTRACT

It was in the 1990s, that the possibility of increased transmission of HIV with the use of injectable contraceptive Depo-Provera®, was first flagged in medical literature. This has posed a challenge for its use in countries, particularly in the African region, where the prevalence and transmission rate of HIV is high. In 2015, a randomised 'clinical' trial, the *Evidence for Contraceptive Options and HIV Outcomes* (ECHO) was launched in four African countries to resolve the question whether the increased risk was causal. Contrary to expectations, the ECHO trial successfully recruited and randomised the specified number of girls/women participants. This paper argues that this was made possible by exercising undue influence, by using incentives, coercive language, and by concealing the real nature of the clinical trial during recruitment. The ECHO trial is unique in subjecting a group of healthy girls/women knowingly to a contraceptive drug with an intention not of finding out whether it is efficacious as a contraceptive, but to find out how risky or life-threatening its use could be. Thus, the ECHO trial has violated one of the central tenets of the Helsinki Declaration by privileging pursuit of knowledge over the interests of the girl/women trial participants from Africa.

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Introduction

The African region records the highest Maternal Mortality Ratio (MMR) in the world, accounting for more than half of the maternal deaths globally each year (WHO Regional office for Africa, 2018, p. 2). A high fertility rate with an associated low prevalence of contraceptive use and unsafe abortions are said to be the major underlying causes with women in the age group of 15–29 years being particularly vulnerable (WHO Regional office for Africa, 2012, p. 20 & 23). Among the several modern contraceptive methods available, the three monthly hormonal injectable contraceptive, Depot medroxyprogesterone acetate (DMPA; Depo-Provera®), has found wide use in Africa with, for instance, nearly half of those using modern methods in sub-Saharan Africa opting for it (Tsui, Brown, & Li, 2017).[1] Though Depo-Provera contraceptive has been in circulation since the 1960s, its approval by the USFDA (United States Food and Drug Administration) took more than three decades because of its potentially hazardous nature.[2] While the USFDA approval was necessary for funding by the USAID, its non-approval did not deter the licensing of Depo-Provera for contraceptive use in other countries. In both South Africa and former Rhodesia (current Zimbabwe), it was promoted by the apartheid regime from the year 1969 onwards (Armstrong, 2017) when it was still in the testing stage.

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However, soon after the USFDA approval in 1992, studies associating Depo-Provera use with increased transmission of HIV began to appear in medical literature raising a serious question on its suitability in populations and countries with high HIV transmission rates. Observational studies indicated a positive correlation between Depo-Provera use and HIV-1 seroconversion in women commercial sex workers from Thailand (Ungchusak et al., 1996) and Kenya (Martin et al., 1998),[3] and increased cervical proviral shedding in previously sero-converted women attending a sexually transmitted diseases clinic in Kenya (Mostad et al., 1997). This implied that not only women in the high risk category had an increased probability of acquiring HIV but their partners too were at an increased risk. In the subsequent years, studies began to investigate this association together with others examining several biologically plausible mechanisms of transmission.[4] In 2012, despite the growing evidence of a positive association, an expert committee of the WHO concluded that,

> … because of the inconclusive nature of the body of evidence on possible increased risk of HIV acquisition, women using progestogen-only injectable contraception should be strongly advised to *also always use condoms*, male or female, and other HIV preventive measures. (Emphasis as in original), (World Health Organization, 2012, p. 1)

Based on this advice, the WHO, under its Medical Eligibility Criteria (MEC), graded Depo-Provera as category 1 contraceptive permitting unrestricted use. However, even though this grading placed no restriction on its use, based as it was on current knowledge and consensus arrived at by multiple stake holders with diverse and conflicting interests, there remained a possibility of this advice being overturned sometime in future. This concern was not without foundation as, despite the reassurance from the WHO, some sub-Saharan countries began to consider withdrawing Depo-Provera from their family planning programmes (Ralph, McCoy, Shiu, & Padian, 2015) as well as debating the policy implications of such withdrawal (see for instance, Jain, 2012).

It was in this context that, in 2012, a consortium, *Evidence for Contraceptive Options and HIV Outcomes* (ECHO) was formed, with initial funding from Bill & Melinda Gates Foundation (BMGF) (Hofmeyr et al., 2018).[5,6] In 2013, the WHO joined the consortium as a member (Hofmeyr et al., 2018). The singular objective of the ECHO consortium was to design and implement a randomised trial to resolve the question, whether the observed increased rates of HIV infection were because of true biological effects or a consequence of methodological limitations inherent in observational studies (Hofmeyr et al., 2018; World Health Organization, 2017a). In 2015, the ECHO study, termed by the Consortium as a 'randomised clinical trial', was posted at ClinicalTrials.gov (Identifier NCT02550067) (Hofmeyr et al., 2018).[7,8] According to the authors, the intention to randomise was based on the premise that, '[t]he gold standard for evaluation of a clinical intervention is a randomized [*sic*] clinical trial (RCT) [*sic*] … ' (Hofmeyr et al., 2018, p. 3). However, as the authors rightly pointed out, because of ethical reasons, a placebo-controlled trial was ruled out as it would have failed to provide contraceptive protection.

Hence, in the ECHO trial, participants were assigned randomly to one of the three selected contraceptive methods, viz., DMPA (Depo-Provera, Pfizer[9]), the LNG sub-dermal implant (Jadelle, Bayer) (both progestin-only hormonal methods), and the intra-uterine device T-380A copper IUD (non-hormonal). Trial participants were recruited from sexually active, HIV negative girls/women, aged 16–35 years,[10] seeking contraception, and not desiring pregnancy for 18 months (the duration of the study). Importantly, they had to be willing to accept a contraceptive method not of their choice, but one of the three methods assigned to them through the randomisation process. The initial plan to include NET-EN[11] as one of the trial arms was dropped on the reasoning that, '[i]f DMPA is found in the trial to have higher HIV risk, it may be important to have an alternative injectable … as an acceptable substitute' (Hofmeyr et al., 2018, p. 6). From this it is clear that, right from the planning stage, there was an implicit understanding that it was Depo-Provera that was being investigated for its association with HIV transmission.

The primary objective of the trial was to compare risks of HIV acquisition with the three methods, with the primary study endpoint being HIV infection as measured by documented HIV

seroconversion occurring post-enrolment (ClinicalTrials.gov, n.d.b).[12] In the ECHO trial, randomisation raised the issue of equipoise. To be in equipoise in a trial is to mean that 'there exists a state of "honest professional disagreement" among medical scientists about which treatment is best' (Nardini, 2014, p. 5). However, in the ECHO trial, the trial was planned to 'settle' the case whether Depo-Provera increases HIV transmission or not. In that sense, women who would be allocated Depo-Provera were being potentially subjected to a greater risk of acquiring HIV. It is perhaps to side-step the thorny issue of equipoise that members of the ECHO consortium (see Hofmeyr et al., 2008; World Health organization, 2017a, p. 10) use the broader term randomised *clinical* trial instead of radomised *controlled* trial.[13] Moreover, the ECHO Consortium uses the acronym RCT for randomised *clinical* trial whereas the acronym is normally used for randomised *controlled* trial that uses a placebo or another treatment as control. Thus, notwithstanding the avoidance of the word 'controlled' to classify the ECHO trial, in reality, it is a randomised *controlled* trial. Here the sub-dermal implant and the IUD act as the control arms for testing the HIV transmission potential of Depo-Provera (the 'treatment' arm). Hence the issue of equipoise is a matter of continued concern in the ECHO trial. This issue will be taken up again later in this paper.

In relation to randomisation, the second issue that the ECHO Consortium had to contend with was the question of feasibility, i.e. whether women would accept a contraceptive method not of their choice and continue with the method for 18 months, the duration of the trial. This problem was surmounted by enrolling only those who were ' … truly willing to using any of the three methods', by 'training and (retraining) [*sic*] study clinicians on contraceptive clinical and counseling techniques', and through follow-up visits (Hofmeyr et al., 2018, p. 7). Screening and recruitment for the ECHO trial began in December 2015 and was completed on 12 September 2017 having randomised a total of 7,830 women (ECHO Consortium, n.d.a) as per the calculated sample size of 7,800 (Hofmeyr et al., 2018, p. 7), from 12 sites: 9 in South Africa, and one each from Kenya, Swaziland and Zambia (ECHO Consortium, n.d.b). The apparent success in recruitment, 'with low refusal rates (data not shown) [*sic*]' (Hofmeyr et al., 2018, p. 7), appears to have circumvented serious doubts raised by others (see, for instance, Ralph, McCoy, Hallett, & Padian, 2013) on the feasibility of randomising women in the ECHO trial.

This paper argues that acceptance of randomisation by the girls/women participants was made possible by exerting undue influence during recruitment and by concealing the real nature of the clinical trial. The paper further argues that the ECHO trial has violated one of the central tenets of the Helsinki declaration by privileging pursuit of knowledge over the interests of the trial participants. The first section examines and deconstructs the process of recruitment; the second examines how well the health needs and interests of the girls/women participants were taken care of, and the third concludes with a discussion on the findings and implications of the ECHO trial.

Deconstructing participant recruitment

The decision to participate in a trial begins at the time of recruitment. The informed consent process is central to getting participants to agree to become research subjects in a trial and involves,

> … three key features: (1) disclosing … information needed to make an informed decision; (2) facilitating the understanding of what has been disclosed; and (3) promoting the voluntariness of the decision about whether or not to participate in the research. (US Department of Health and Human Services, n.d., unpaged)

In the ECHO trial girls/women were recruited directly through clinics by self-referral, but respondent driven recruitment was an additional method in sites performing peer to peer recruitment (FHI 360 Study #523201, 2017a). At the time of enrolment, girls/women participants were administered an informed consent form that included the following clause:

> PEER to PEER RECRUITMENT [*sic*]

> Please indicate whether you would like to be considered for our peer to peer recruitment program. If willing, you will be offered a maximum of three referral coupons to give to your friends who may be willing to participate in the ECHO study. You will receive <local amount>[*sic*] for each referral who walks in the clinic [*sic*] for the screening process with a referral coupon given to them by you. (FHI 360 Study #523201, 2017a, p. 12)

The recruiter's fee was in addition to the other payments that were due to the participants. Peer driven recruitment is not mentioned in the Hofmeyr et al. (2018) paper. Some of the ethical concerns identified with this method of participant recruitment are exploitation of the trust of peers in trying to meet recruitment quotas, potential for 'egregiously' violating privacy and confidentiality, (Simon & Mosavel, 2010, p. 2), risks such as relationship conflict, loss of friendship, and violence (Mosher, Moorthi, Li, & Weeks, 2015, p. 1). Moreover, as Simon and Mosavel (2010, p. 9) point out, '[a] recruiter's personal experience is not … an acceptable framework for conveying the risks and/or benefits of participating in research'. Adding to the issue of trust and conflict of interest is the personal financial benefit the peer recruiter stands to gain which the recruitee is most unlikely to be aware of. The practice of paying recruiters, termed as 'finder's fee', has been rejected as unethical by several professional organisations such as the American College of Physicians and the American Medical Association (Boozang et al., 2009; Brown, 2000, p. 9), by pharmaceutical companies such as Pfizer, and is considered 'a kickback under [American] federal and state laws' (Boozang et al., 2009, p. 11 & 12). Finder's fee is illegal in California (Office of the Human Research Protection Program, 2019, p. 4).[14] Peer driven recruitment in the ECHO trial therefore raises the issue of differential ethical standards between the global north and the global south. In effect, this reflects the cynical attitude of the sponsors towards the low socio-economic status of the girl/women participants who are all from the African countries.

As much of the recruitment in the ECHO trial was carried out in health centres, it raises other ethical issues as '[u]ndue influence and exploitation may happen when potential participants are approached by persons in a position of authority. Any relationship of dependency – including even between a physician and a participant – may give rise to unjustified influence' (Karlberg & Speers, 2010, p. 70). Additional conflict of interest is present when the treating physician is also the research investigator. To avoid this and in the interests of the trial participants separation of the two roles has been recommended (Brown, 2000), a recommendation that does not appear to be part of the guidelines in the ECHO trial.

Provision of incentives is another way to induce participants to accept randomisation. Feldblum et al. (2005) note that even 'small' financial gains, for instance, transportation costs and offer of free STI tests and treatment, were found to be important incentives for recruitment into a randomised trial. In Kenya, one of the countries included in the ECHO trial, it has been documented that people participated in clinical trials because this was often the only way by which they could access health care services (Wemos, 2017). In the ECHO trial, participants were offered reimbursement at the time of the screening visit (FHI 360 Study #523201, 2017b), enrolment visit, follow up visits, with the amount calculated on the basis of 'travel to the study clinic, meals, time spent at the clinic', and 'inconvenience caused … when taking part in the research' (FHI 360 Study #523201, 2017a, p. 9 &10). Further, in centres that had the local Institutional Review Board's (IRB) approval, additional reimbursements or 'gifts' were offered for remaining in the study 'as a courtesy for completing all study visits and procedures', and, in sites 'participating in studies of biological mechanisms', for agreeing to additional sample collection (FHI 360 Study #523201, 2017a, p. 10). The amount of money offered varied as it was left to the discretion of the local IRB and Ethics Committee. The participants were also offered free treatment for infections detected at the time of enrolment.

It is clear from the above that the amount of monetary compensation offered to the participants of ECHO trial could very well have been substantial enough to incentivise 'participation'. Considering the poor socio-economic context from which these participants are drawn from it raises doubts about the nature of their 'voluntary' participation. In general, monetary reimbursement of costs incurred by participants in clinical trials has come to be accepted as a norm. However, in the

ECHO trial the issue is whether such reimbursements and incentives were compelling enough for them to accept randomisation and stay on till the completion of the study. All that can be said at this point is that only by making public, the amount disbursed as reimbursements and gifts can a definitive statement be made on the role of such monetary gains.

Participant recruitment: Consent as moral duty

In the ECHO trial, signed informed consents were taken from participants twice: once at the time of screening (FHI 360 Study #523201, 2017b), and again, at the time of enrolment (FHI 360 Study #523201, 2017a).[15] The screening Informed Consent (IC) form template is 8 pages long and that of enrolment IC form, 17 pages.[16] A manual used in ethics training by FHI 360, the sponsor of the ECHO trial, states that the informed consent materials should use local language, be written for appropriate reading level, and illustrated with appropriate concepts and images (Rivera & Borasky, 2009, p. 32).[17] The same manual also recommends that a translation and back translation be performed and pilot tested before finalising them. It is unclear from any of the relevant documents[18] whether these principles, especially translation into the local language were applied in the ECHO trial. It is noteworthy that only in a few places in the enrolment IC form template, for instance, pertaining to reimbursement, does it state explicitly, within parenthesis, 'additional local language … here' (FHI 360 Study #523201, 2017a, p. 10). In both templates, the binary classification of participants' literacy level as 'literate' or 'illiterate', does not provide the level of literacy of the 'literate' participant. Therefore the comprehension of the participant as 'literate' could mean anything upward from primary school educational level. However, it is more than likely that majority of the participants were not of a literacy level to understand the consent forms.

The core purpose of IC is to stress the entirely voluntary nature of participation in the trial. The text in the IC forms becomes crucial in assessing how well this is operationalised. The following excerpt taken from the ECHO trial's enrolment IC form (FHI 360 Study #523201, 2017a) that appears right in the beginning of the consent form (Introduction, paragraph 3) could be considered indicative of the language used to persuade a participant to enrol in the trial.

> 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 be in the study for the entire 18 months. If you and many others decide to leave the study early, it will hurt 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 (FHI 360 Study #523201, 2017a, p. 2).

Table 1 provides a textual analysis of the above quote to reveal the underlying sub-text.

The analysis of the text from the enrolment IC form (Table 1) shows undue pressure was brought to bear on the individual girl/woman participant by evoking a sense of misplaced responsibility for remaining in the trial to benefit others. The tone implies responsibility for remaining in the trial, short of *force majeur,* and a sort of 'moral responsibility' for the trial on the part of participants who have to carefully consider their decision. Yet the core purpose of any informed consent form is not to invoke vague 'duties' of girls/women participants towards the quality of the study or potential beneficiaries in the future. This sentiment is repeated several times in the IC forms. For instance, under the sub-heading 'Benefits of study participation', the participant is told '[p]articipating in this study may help others in the future by increasing knowledge on contraceptive methods' (FHI 360 Study #523201, 2017a, p. 8),[19] and under 'Disontinuation of your study contraceptive method', ' … you should understand that, if you start and stop using your study contraceptive, it will be difficult to answer the study question' (FHI 360 Study #523201, 2017a, p. 9).

Continuing with textual analysis of the contents of the IC Forms, the screening form template has this to say about randomisation, one of the contentious issues in the trial and a difficult concept to explain:

Table 1. Textual analysis of an excerpt from ECHO template enrolment informed consent form[a].

Text	Comment
If you join, you have the right to stop the study at any time you *choose*. (italics added)	This sentence does not make sense as the participant cannot stop the study. Further, the use of the word 'choose' renders leaving the study as a deliberate considered act, whereas the need to leave could be due to unforeseeable personal circumstances, or a serious drug reaction, where neither is a matter of 'choosing'. Leaving the trial for such reasons, if framed as 'choice', has the potential to manipulate by guilt tripping the participant. A more ethical and accurate wording, less linked to the 'guilt' trope, which should have appeared on page 1 of the consent form appears on page 8 of this document '[t]aking part in this study is voluntary. If you decide to take part, you can stop at any time without saying why'.
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 be in the study for the entire 18 months. (italics added)	'Believe: Accept that (something) is true, especially without proof'.[b] It is unclear how a potential trial participant can give the assurance at the start of a trial that she is able to commit to being in the study for 18 months. In any case, if the trial is voluntary why should she need to *believe* that this will be the case? Even prior to starting the trial, the onus of the trial succeeding has been placed squarely on the trial participants' shoulders. One of the important criterion for recruitment, that the girl/woman should not be planning to get pregnant in the next 18 months, is missing.
If you and *many others* decide to leave the study early, it will *hurt* 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. (italics added)	By evoking the behaviour of 'others' (who are not party to the individual consent form that is to be signed by an individual) and adding the word 'many', the act of a single girl/woman (were she to leave) is unethically and unjustifiably embedded as part of a 'collective' act. The use of the emotive word 'hurt' as the stated outcome of leaving early, allocates to the girl/woman involved a share of potential collective responsibility (even blame or guilt) for the 'painful' damage that could hypothetically be done to the quality of the study results. Moreover in this context, the inanimate 'results' attain the characteristic of a living thing as it can now be 'hurt' by the act of leaving. In essence, this sentence, in tone and content, is contradictory to the first sentence that states 'you have the right to stop' and cancels out that right, thereby manipulating the participant to believe that it is her/their individual and collective duty to remain.
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. (italics added)	By tying the need to provide an accurate answer to an altruistic motive of helping millions of faceless women the participant does not know, undue moral pressure is being brought on the individual girl/woman participant to remain in the study. The phrase 'think about this carefully' does not sound advisory; it contains an underlying implication of threat. In this case the negative consequences are for the study, but it is suggested that it affects innocent others, the 'millions of women'. In relation to the participant girl/woman, it enables the researchers to take a moral high ground as enforcer of altruism.

[a]Text from FHI 360 Study #523201 (2017a, p. 2, point 2).
[b]English Oxford Living Dictionaries (n.d).

> … we will give you one of three contraceptives: the DMPA injections, the Jadelle implant, or a copper IUD. You will not choose your method. We will also not choose your method. A computer will make this choice by chance (like flipping a coin or throwing a dice) [*sic*]. You will have the same chance of getting any one of the three contraceptive methods. (FHI 360 Study #523201, 2017b, p. 3)[20,21]

The role of a computer in randomisation has been known to be misinterpreted by patients and their relatives (in this trial, the guardians) as a computer is perceived to be more competent 'at deciding

what [is] best for them' (Jepson et al., 2018, p. 78). The same study found that the use of metaphors associated with gambling (dice- throwing) problematic to patients. A more troubling finding from a review of studies on the ethics of randomised trials was that 'patients [did] not always understand that they had been randomised to a control group which was just what the doctors had anticipated' and '[w]orse, doctors seemed to have been aware that patients may not have fully understood what was going on. For many, informed consent seemed a little more than a ritual' (Edwards, Lilford, & Hewison, 1998, p. 1211 & 1212).

Recall of concepts such as randomisation after four to twelve months was only 19% in a trial that had recruited participants from impoverished non-white communities from outside Cape Town, South Africa (Moodley, Pather, & Myer, 2005). This was despite the fact that explanations prior to recruitment had been at three levels: the community, the group and the individual. In the ECHO trial explanations were given only at the individual level during enrolment and if probability of recall is taken to be an indicator of internalising this information, recall in the ECHO trial could very well be lower than the above cited study from Cape Town.

Importantly, the consent forms do not spell out the implications of randomisation. The primary goal of this trial, which is to find out if use of Depo-Provera contraceptive increases the chances of getting infected with HIV or not because evidence suggests that it could, is also the most contentious part of this trial. The IC forms explain it as follows:

> The main goal of the ECHO study is to see if the risk of getting HIV is *different* with three different contraceptives. (Emphasis added) (FHI 360 Study #523201, 2017a, p. 3, 2017b, p. 2)

> The ECHO study is designed to help us understand if any of these three contraceptive methods *change* a woman's risk of getting HIV. We need to do this study because we do not know if use of the DMPA injection, the Jadelle implant, or the copper IUD *has an effect on the risk* of getting HIV. (Emphasis added) (FHI 360 Study #523201, 2017a, p. 3, 2017b, p. 3)

Further, in answer to a question that they pose, '[w]hat do we know about these three contraceptive methods and the risk of getting HIV?', the consent forms state:

> The DMPA injectable: The World Health Organization (WHO) [*sic*] – a global group that coordinates international health information – states that there is evidence of a possible increased risk of HIV acquisition associated with DMPA. However, not all studies have found this association and there is uncertainty about whether DMPA causes increased HIV risk. WHO indicated that women at high risk of acquiring HIV can use DMPA because *the advantages of this contraceptive method outweigh the possible increased risk of HIV*. WHO has also said that better research is needed to resolve this *uncertainty*. (Emphasis added) (FHI 360 Study #523201, 2017a, p. 3, 2017b, p. 3)

Even a 'literate' adult participant could have difficulty in understanding the above excerpt which is in a convoluted language and uses concepts such as 'risk' and 'acquisition'. Further, by evoking the authority of the WHO several times, the trial sponsors hope to buttress and justify the ECHO trial as a mandate from the WHO. However, a careful reading of the above excerpt shows that the WHO recommendation has been altered in important ways. In December 2016, while the recruitment for the ECHO study was underway, based on new evidence from a meta-analysis by Polis et al. (2016), WHO changed the MEC of Depo-Provera from category 1 (unrestricted use) to a more cautious category 2 (advantage outweighs disadvantage). The Guideline Development Group of the WHO stated,

> [w]omen at high risk of acquiring HIV *can also* use progestogen-only injectables (norethisterone enanthate [NET-EN] and depot medroxyprogesterone acetate [DMPA, intramuscular or subcutaneous]) [*sic*] because the advantages of these methods *generally* outweigh the possible increased risk of HIV acquisition (MEC category 2) [*sic*]. (Emphasis added) (World Health Organization, 2017a, p. 2)

The WHO clarified further that '[a]ll individuals at high risk of HIV or other STIs need ready access to infection prevention strategies such as condoms and, where appropriate, pre-exposure prophylaxis' (World Health Organization, 2017b, question 5). Thus, the WHO's most recent ruling did

not unequivocally state that Depo-Provera was safe as the Informed Consent forms of the ECHO trial imply. In fact, the WHO in another of their report states clearly that, '[b]ased on the consistency and precision of the evidence, and the coherence of the studies of DMPA versus non-hormonal contraception and DMPA versus NET-EN, the evidence was *upgraded from low to low-to-moderate*' (emphasis added) (World Health Organization, 2017a, p. 8).

Moreover, the WHO ruling in itself was problematic as it clubbed both DMPA and NET-EN together as progestogen-only contraceptives, whereas, the meta-analysis by Polis et al. (2016, p. 2665) had concluded that, '[n]ew information increases concerns about DMPA and HIV acquisition risk in women … Data for other hormonal contraceptive methods, including norethisterone enanthate, are largely reassuring'. A more accurate and ethical ruling of the WHO would not have classified DMPA and NET-EN under the same category when the risk linked to HIV acquisition was evidently different. Where the ECHO trial is concerned, notably, the WHO came out with the new relatively cautious recommendation in December 2016 when recruitment for the trial was underway. It is not clear how this altered the recruitment process.

Thus, while the IC forms state that each of the participants will have the same chance of being allocated one of the three methods under research, what is not made explicit is that the participants may not have the same chance of becoming HIV positive over the course of the trial or later. The potential for increased risk with DMPA raises the question of equipoise, mentioned earlier in this paper. This concern was flagged by others too (Ralph et al., 2013) even before the ECHO trial was launched: do women in the three arms have equal chances of getting HIV infection? In a presentation made on behalf of the ECHO Consortium, 'highest risk' with DMPA was stated to be one 'possible scenario' in the ECHO trial (Baeten, 2016, slide 11). Hence, for the girls/women participants who were allocated Depo-Provera through randomisation, at the initiation of the trial, there was a reasonable doubt/uncertainty of an increase in the probability of acquiring HIV infection as compared with the girls/women allocated the other two contraceptive methods. Thus, it cannot be denied that one third of the trial participants who received Depo-Provera were knowingly subjected to a drug with potentially fatal outcome. In this trial, HIV acquisition was not the only health risk that the girls/women participants faced. The three contraceptive methods in the study have been in use for a considerable period of time and are known to have serious health effects that could be fatal or lead to life-long disability. This does not appear to have been a major consideration in the ECHO trial. The next section examines how the ECHO Consortium addressed the health issues of the girls/women arising as a consequence of participating in the trial.

Risking lives but abdicating responsibility

The European Medicines Agency defines Adverse Events (AE) as

> … any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product. (European Medicines Agency, 2004)

The USFDA defines Adverse Drug Reaction (ADR) as ' … any adverse event for which there is a reasonable possibility that the drug caused the adverse event' (US Food and Drug Administration, 2018). Surprisingly, the protocol does not provide a standardised list of ADRs that are already known to be associated with the contraceptives tested that the researchers must refer to.[22] In the ECHO trial protocol, under 'Risks', it is asserted that '[i]t is not expected that this trial will expose human subjects to unreasonable risk' (ECHO Consortium, 2017, p. 42). But scattered through the protocol document, are a few well-known serious ADRs. These are HIV seroconversion (p.25), deep vein thrombosis and pelvic infection unresponsive to treatment (p.24), severe allergic reactions (p. 22) and uterine perforation (p.42). Moreover, there is a discordance between the ADRs presented

in the IC Forms and the trial protocol. For instance, in the enrolment IC Form (FHI 360 Study #523201, 2017a, p. 7) ectopic pregnancy is mentioned with the use of sub-dermal Implant. This is missing from the ECHO trial protocol in the section on sub-dermal implant but is mentioned under Copper IUD (p. 13); uterine perforation is mentioned in the protocol but is missing from the IC form.

The ECHO trial also underplays the potential risks to some of the other serious ADRs. For instance, with regards to DMPA use, the IC Form states, '[t]hinning of the bones may occur, but will go back to normal when you stop the injections' (FHI 360 Study #523201, 2017a, p. 7), which is missing from the trial protocol. However, Pfizer, the manufacturer of Depo-Provera gives a Black Box warning in their product information in Canada noting that, ' … use of DEPO-PROVERA [*sic*] has been associated with loss of bone mineral density (BMD) [*sic*] which may not be completely reversible. Loss of bone mineral density is greater with increasing duration of use' (Pfizer Canada Inc., 2018, p. 5). In fact, the pharmaceutical company Pfizer appears to be more 'ethical' in listing out ADRs under 'serious warnings' in their product information material in Canada than the sponsors of the ECHO trial towards their participants from the four African countries.

Instead, under the sub-heading, 'Adverse Event Relationship to Study product', the trial protocol states, '[t] he on-site investigator/designee will assess whether an AE is related to the study agent using the available information about the study products and his/her clinical judgment' (ECHO Consortium, 2017, p. 39). This is against the tenet that multicentre trials, 'to be meaningful, … must be conducted in the same way at all study sites. *Procedures must be standardised, as well as evaluation criteria*' (emphasis as in original) (Karlberg & Speers, 2010, p. 57). In the ECHO trial which is an open-label study, in the absence of standardisation, leaving assessment and recording of AE and ADRs to the discretion of the local investigator, would result in a serious bias difficult to quantify. Further, though, the protocol states that all AEs regardless of severity or presumed relationship to study product are to be documented, only those that are considered serious or resulting in method discontinuation are to be recorded on the 'Case Report Form' (ECHO Consortium, 2017, p. 39). The absence of a standardised list of ADRs across sites and the manner of selective recording has implications for the care and rights of the trial participants.

The most surprising finding is a near absence of care provided to the trial participants. Table 2 describes the care offered to the participants as set out in the enrolment IC Form. It is clear from table 2 that for all practical purposes, the sponsors of the study have accepted no responsibility for the care of the participants even were they to sero-convert (become HIV positive) during the trial, the primary endpoint of the study and potentially fatal outcome. However, the trial protocol states that sero-converters were asked to remain in the study until completion of the follow-up period in order to continue data collection relevant to secondary outcomes (ECHO Consortium, 2017, p. 25). What does come across clearly is the callous and cavalier manner in which the well-being of the participants is side-lined in pursuit of knowledge. The ECHO Consortium appears to be interested in their research 'subjects' only as long as their bodies can provide the necessary data. The physical, psychological, social and economic consequences of participating in the trial, particularly if the participant becomes HIV positive, is thus left to be borne by the girl/woman participant, her partner, family members and the health system of the country where the trial is being conducted. It is unlikely that these standards of care would be acceptable if this trial were to be conducted in a country from the global north, for instance the USA, where the main funders and sponsors of the study are located. Such double standards are not new. In 1983, in the context of the USFDA's denial for licensing Depo-Provera, Malcolm Potts of Family Health International (precursor to FHI360) in a co-authored paper observed, 'that the criteria used by the FDA must apply to the developing world (at the risk of indulging in hyperbole) [*sic*] would be for a committee to design a mousetrap while the village is being attacked by a tiger' (Potts & Paxman, 1984, p. 18). Three decades down the line, this rationale continues to inform and justify dual ethical standards of contraceptive drug testing and promotion prevailing in the global north and the global south.

Table 2. Care offered to participants of the ECHO trial for health issues arising in the course of the trial[a].

Health problem	Care offered by the ECHO Consortium	Remarks
If you become pregnant:	We will ask you to stay in the study and we will refer you to a local service provider for pregnancy care. You will be responsible for your pregnancy healthcare.	The ECHO trial's secondary endpoint is pregnancy. Therefore, to not provide care for women who become pregnant during the course of the trial is unethical. It is also not clear whether safe abortion services were to be provided where it is permissible by law.
If you become HIV positive during the study	We will 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 <Add site specific language to explain if those costs are included in a national program> [*sic*]	HIV acquisition is a primary endpoint of this study and could be considered a major, potentially fatal ADR. The decision not to provide care or bear the cost of care is unethical and in violation of the Helsinki Code.
	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 or referral for any curable infection that is passed by sex.	This is a clear indication that the sponsors of the study will provide free treatment only for STDs and not HIV. The participants were offered free treatment for infections detected at the time of enrolment; however this was a trial protocol need.
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 were enrolled in this study and inform us as well.	There is no mention of providing care or financial assistance in these instances. In fact this information is being sought as part of data requirement and not because of the concern for the trial participant.
Financial arrangements	You will not pay for study medication, study visits and procedures.	Though this is framed as 'care', this is no largesse on behalf of the sponsors of the study as in any case these are part of the trial need.
	The study will cover costs of direct medical care for complications related to the study.	Since no list of such complications is provided in the informed consent form or in the protocol, what would be covered under this clause is arbitrary and left to the discretion of the local investigator.
	All reversible contraceptives have a small chance of pregnancy, which is not considered a complication.	But it is considered contraceptive 'failure' and forms part of the study objectives and end points. This also raises the issue of access to abortion services where it is permissible.
	We will not treat any disease or condition not related with the study, but we will refer you for the correct care and treatment	Since a standardised list of such disease or condition related to the study is not provided, in the IC form or in the protocol, what would be covered under this clause is arbitrary and left to the discretion of the local investigator

[a]The text in column 1 and 2 are direct quotes from the document. Original text in column 1 is in uppercase.
Source: Enrolment Informed Consent Form (FHI 360 Study #523201, 2017a, p. 6 and 9).

Discussion

Thus far, this paper has argued that the ECHO trial was able to recruit and randomise girls/women by exercising undue influence, by using coercive language and by concealing the true objective and implications of the study from the participants. It has been shown that the concern of the sponsors appear to lie more with the collection of data than with the interests and needs of the girls/women who have been treated as objects rather than as participants. Three reasons could be put forward to explain why such low ethical standards adopted in the ECHO trial have not come under greater scrutiny so far.

First, unlike a drug trial operationalised by a pharmaceutical company, the ECHO trial is helmed by institutions and individuals who are deemed to be unconnected with commercial interests. However, this may not be strictly accurate. The trial protocol states that '[t]here are no conflicts of interest to declare' (ECHO Consortium, 2017, p. 45). However, Hofmeyr et al. (2018) declare that the funders had a role in the design of the study. BMGF, the first and the main funder of the ECHO study, has financial interests in the pharmaceutical companies of the products being tested. In 2002, BMGF had

invested in shares in nine big pharmaceutical companies including Pfizer, the manufacturer of Depo-Provera (Bank & Buckman, 2002). In 2014, BMGF signed an agreement with Pfizer to subsidise the sale of the injectable Sayana press which is a new delivery system to inject DMPA (Pfizer, 2014) and in 2016, Pfizer was awarded a grant by BMGF for vaccine development (Pfizer, 2016). In 2013, BMGF and Bayer (manufacturer of Jadelle, the sub-dermal implant) signed a 'Jadelle Access Program' through which Bayer would supply 27 million contraceptive implants in seven years with BMGF 'covering the risk of default' (Bayer, n.d.). With regards to academic institutions, the BMGF is so deeply entrenched in medical research through funding studies and clinical trials, that the association has ceased to be viewed as a conflict of interest.[23] In 2010, the BMGF was funders of an unethical trial with HPV vaccine on adolescent girls in India which resulted in deaths and serious injury (Parliament of India, 2013). The BMGF is also the largest private donor of the WHO (Saez, 2017), a member of the ECHO Consortium. As far as the WHO is concerned, in the mid-1980s, it was involved in the unethical testing of hazardous contraceptives particularly the injectable contraceptives in India (Sathyamala, 1998). On this basis, it was argued that the WHO cannot be treated as a 'neutral' scientific body because its interests lay with the population control lobby and the pharmaceutical companies (Sathyamala, 1998, p. 196).

The second reason for a lack of scrutiny could be that the ECHO Consortium was able to sell the idea of the trial by repeatedly emphasising its superior 'science' for having adopted the randomisation design. According to the ECHO Consortium, due to the randomisation design, the trial would provide the 'highest quality [of] evidence to resolve … important public health question' (Hofmeyr et al., 2018, p. 8). The term 'robust evidence' appears repeatedly in the publications by members of the Consortium (see Cates, 2014; Hofmeyr et al., 2018; Rees & ECHO Consortium, 2014). However, Deaton and Cartwright (2018, p. 2) argue that it is unreasonable to expect one RCT to settle any question and that

> RCTs can play a role in building scientific knowledge and useful predictions but they can only do so as part of a cumulative program, combining with other methods, including conceptual and theoretical development, to discover not 'what works', but 'why things work'.

Therefore, one RCT such as the ECHO study will not 'settle' the issue but will only add to the evidence that is already accumulated through more than two decades of research. Moreover, mere randomisation does not protect against selection bias in the acceptance or rejection of participants into a trial. Specifically, the ECHO trial is an open-label study, a design known to have selection bias (Kahan, Rehal, & Cro, 2015), observers' bias, reporting bias, and ascertainment bias (Forder, Gebski, & Keech, 2005), none of which can be eliminated through mere randomisation.

Importantly, because of the Consortium's assertion of 'superior' science other critical aspects of the trial have also gone unremarked. For instance, the trial is designed to have 80% power to detect 'at least' a 50% increase in risk of HIV acquisition with a 5% dilution effect due to method switching (Hofmeyr et al., 2018, p. 7). The most recent meta-analysis of observational studies suggested that were the association to be causal, the risk could be 50% or less (Polis et al., 2016).[24] By choosing a cutoff point of 50% risk for sample size calculation, a decision has been made not to detect smaller risks (Hofmeyr et al., 2018, p. 4). This makes little sense either for the individual girl/woman or from a public health perspective. A modelling exercise for assessing the implications of a risk of HIV acquisition showed that if risk of HIV infection increased by 1.2–2.19 fold, '[g]lobally, a total of 27,000–130,000 new infections per year (for RR = 1.2 −2.19) [*sic*] would be attributable to IHC [Injectable Hormonal Contraceptives], 87-88% of which occur in southern and eastern Africa' (Butler et al., 2013, p. 4). The authors concluded that if there is a true association even with as low as 1.2 folds increased risk of HIV transmission, reducing the use of DMPA would reduce new infections substantially. This would result in public health benefit in countries in southern Africa, despite its high maternal deaths.[25] While such modelling exercises could be meaningful for policy formulation, a higher risk of HIV acquisition has different implications for the girl/woman trial participant. This is because unlike most drug trials where the participant is a person with a disease for which the drug is being tested for, in the ECHO trial, as in all the other trials on

contraceptive drugs, the contraceptive drug(s) are being tested on healthy women. Therefore the 'risks' they are being subjected to are on par with that of healthy volunteers in Phase I or II of general drug trials. Therefore the need for care and protection of such participants is higher than that of Phase III drug trials on patients with specified disease. The added issue in the ECHO trial is that the primary end-point is in itself a serious ADR with potentially fatal outcome. Thus, for the first time in the history of clinical drug trials, the ECHO trial is unique in subjecting a group of healthy girls/women knowingly to a contraceptive drug with an intention not of finding out whether it is efficacious as a contraceptive, but to find out how risky or life-threatening its use could be. In other words, this trial has the potential of making the healthy bodies of trial participants into 'diseased' bodies as the consequence of participating in the trial.

This raises the third and perhaps the most important reason for the scant attention paid to the ethics in this particular trial. Countries in the global south do not have stringent regulations for clinical trials or robust regulatory mechanisms (Wemos, 2017) as compared with countries in the global north. Moreover, the ECHO trial participants were girls/women from impoverished communities with little recourse to having their voices heard. These, together with the epistemic authority wielded by the global north, have resulted in the near absence of counter-narratives at both the academic and civil society levels to challenge the ethics, or the lack of it, in the ECHO trial.

Concluding remarks

The Helsinki Declaration, No.8, General Principles, states unequivocally, that '[w]hile the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects' (World Medical Association, 1964). This paper has demonstrated that the ECHO trial was possible only by misleading and misrepresenting important information to the girls/women who were recruited. By not providing any care or legal protection to the participants, the sponsors have shown total disregard to the health and wellbeing of the girls/women from the global south. The ECHO trial has violated one of the central tenets of the Helsinki Declaration by privileging science over the interests of the trial participants. It is now for the health authorities of the four African countries that have participated in the ECHO trial, as well as the larger medical-scientific community, to take cognisance of the gross violation of the rights of the girls/women participants in the name of science and find suitable remedies, legal and otherwise. A first step towards this could well be to set up an independent enquiry to investigate the ethical concerns raised in this paper.

Notes

1. This is partly donor driven. For instance, in 2016, countries in Africa received 79% of the USAID shipment of contraceptive (U.S. Agency for International Development, 2017) and, in 2017, more than 60% of UNFPA (United Nations Population Fund) contraceptive funding (UNFPA, 2017). Injectable contraceptives formed a sizeable amount of these procurements.
2. These included its potential carcinogenic, teratogenic and mutagenic effects (see Sathyamala, 2000). See Multinational Monitor (1985), for details of the USFDA report by the then Commissioner Donald Kennedy rejecting the parent company Upjohn's first application.
3. These two studies were prospective studies.
4. Mechanisms postulated for the increased HIV transmission are, increased HIV viral replications, effects on local genital tract physiology due to lowered estrogen levels and changes in immune response (Hickey, Marino, & Tachedjian, 2016). For a recent excellent review of the mechanisms for increased transmission see Hapgood, Kaushic, and Hel (2018).
5. The ECHO consortium was formed by representatives of the US based FHI360, the University of Washington, the University of the Witwatersrand Reproductive Health and HIV Institute (Wits RHI) , and the BMGF. Apart from the BMGF, funding comes from the USAID, the Swedish International Development Cooperation Agency (SIDA), and the Medical Research Council of South Africa (Hofmeyr et al., 2018). In addition, UNFPA is also a funder of this trial (ECHO Consortium, 2017, p. 5), and it is part of the EDCTP2 programme supported by the European Union (Human Reproduction Programme, 2018).

6. Hofmeyr et al. (2018) is the authoritative summary of study protocol of the ECHO trial on behalf of the ECHO consortium. It was first published on 29 December 2017 with the latest update, as of November 2018, on 16 July 2018. The paper was published in *Gates Open Research* after an open peer review by two referees.
7. ClinicalTrials.gov is a US database of privately and publicly funded clinical studies conducted around the world. The website makes it clear that '[l]isting a study on this site does not mean it has been evaluated by the U.S. Federal Government. The safety and scientific validity of a study listed on ClinicalTrials.gov is the responsibility of the study sponsor and investigators' (ClinicalTrials.gov., n.d.a).
8. According to the ECHO trial protocol the trial was to be registered with the World Health Organization as part of their clinical trial database (ECHO Consortium, 2017, p. 42). However there is no reference to this in the paper by Hofmeyr et al. (2018). Only on 2 November 2018, was it included in the 'Current project brief' issued by the WHO (Human Reproduction Programme, 2018).
9. In 1995, Upjohn, the parent company of Depo-Provera merged with Pharmacia and subsequently, in 2003, Pharmacia merged with Pfizer.
10. This paper will use the term 'girls/women' to reflect the age composition of the participants. In the ECHO trial protocol, participants aged less than 18 years are termed varyingly as 'women', 'adolescents', 'young women', and 'minors' (ECHO Consortium, 2017, p. 17, 19, and 44). Hofmeyr et al. (2018, p. 4) refer to the participants aged 16–35 years as 'women'. It is not clear how many of the centres recruited participants aged less than 18 years; all that is stated is 'where permissible by national regulations and local IRB approval' (ECHO Consortium, 2017, p. 18).
11. NET-EN (norethisterone enanthate) is a two monthly progestogen-only injectable hormonal contraceptive similar to Depo-Provera.
12. The secondary objectives of the ECHO study are to compare pregnancy rates, rates of adverse events leading to discontinuation and continuation rates among the three methods (Hofmeyr et al., 2018). The tertiary objectives are to evaluate whether age and HSV-2 (herpes simplex virus – type2) infection 'modify the hormonal contraception and HIV acquisition relationship [and] to evaluate the effect of contraception on early HIV disease progression among seroconverters' (Hofmeyr et al., 2018, p. 3). However, sample size calculations were based on estimating only the primary end point and therefore, may not have the necessary statistical power to evaluate the secondary and tertiary objectives.
13. See MRC Clinical Trials Unit (n.d) for a description of RCTs.
14. Ethical guidelines developed by the Council for International Organizations of Medical Sciences in collaboration with the WHO does not mention peer-driven recruitment and refers to finder's fee only in relation to researchers (Council for International Organizations of Medical Sciences, 2016).
15. According to the study protocol, in centres recruiting girls (aged less than 18 years), ' … study staff will *seek* parental/guardian consent as well as assent from the minor participants' (emphasis added) (ECHO Consortium, 2017, p. 44), making it somewhat ambiguous whether parental/guardian consent was mandatory or not.
16. The screening IC form template has 6 pages of information and the enrolment IC form template has 10 pages.
17. FHI360, the coordinator of the ECHO study has funded this manual and holds the copyright. However, there is a disclaimer, that '[t]he information contained in [the] publication does not necessarily reflect … FHI 360 policies' (Rivera & Borasky, 2009, p. 5).
18. The two Informed Consent form templates, the supplementary document and paper by Hofmeyr et al. (2018).
19. This framing is also vague as the ECHO trial is about the risks of the three study contraceptives only.
20. In the enrolment IC form template the wording is 'choose your method by chance' (FHI 360 Study #523201, 2017a, p. 4).
21. Note that the implant is mentioned by its brand name while the other two methods are not.
22. The 'Investigator Brochure(s)', mentioned in the 'Investigator Signature Form' of the trial protocol (ECHO Consortium, 2017, p. 5), do not exist.
23. For instance, both Vermund (2015) and Pettifor (n.d.) who 'open' refereed the Hofmeyr et al. (2018) paper and had declared no conflict of interest were former recipients of grants from the Gates Foundation.
24. Though, the result was not statistically significant, some of the observational studies showed a hazard ratio ranging from 1.27 to 1.34 (Polis et al., 2016).
25. Although Hofmeyr et al. (2018) have cited the study by Butler et al. (2013), the implications for countries in southern Africa has not been included. Were DMPA to be discontinued, the increase in maternal deaths by 18,000 is far less than 27,000 new HIV infections with just 20% increased risk.

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