PAPER

Undue inducement: a case study in CAPRISA 008

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ABSTRACT

Participant safety and data integrity, critical in trials of new investigational drugs, are achieved through honest participant report and precision in the conduct of procedures. HIV prevention post-trial access studies in middle-income countries potentially offer participants many benefits including access to proven efficacious but unlicensed technologies, ancillary care that often exceeds local standards-of-care, financial reimbursement for participation and possibly unintended benefits if participants choose to share or sell investigational drugs. This case study examines the possibility that this combination of benefits may constitute an undue inducement for some participants in middle-income countries, where economic challenges are prevalent. A case study is presented of a single participant in a cohort of 382 participants who used concealment, fabrication and deception to ensure eligibility for a post-trial access study of an unlicensed HIV prevention technology at potential risk to her health and that of her fetus. A root cause analysis revealed her desire to access HIV prevention during an unplanned pregnancy with a partner whose faithfulness was in question. Researchers should consider implementation of systems to efficiently identify similar cases without inconveniencing the majority of participants

Trial registration number NCT01691768.

INTRODUCTION

Young women in sub-Saharan Africa have a disproportionately high prevalence of HIV,[1] making research on women-initiated and controlled methods of HIV prevention crucial. Compounded vulnerability consequent to reduced ability to negotiate safe sex practices with partners,[2 3] limited access to affordable proven HIV prevention therapies[4] and economic challenges which undermine autonomy and increase dependency on others increase the possibility that participation in these trials may lead to an increased perception of undue inducement. This perception could be held by Research Ethics Committees (RECs), investigators or other stakeholders, such as community advisory boards.

Inducement is considered undue only if all of the following criteria are met: (1) a desirable good is offered; (2) this offer is large and excessive enough to be irresistible within the context; (3) the offer leads to poor judgement in an important decision; (4) the decision leads to a sufficiently high probability of harm. Not all inducements are undue.[5 6] Independent ethics review is a key element in ensuring that trials are free of undue inducements.[6] However, independent ethics review cannot always anticipate the unique behaviours of particular individuals whose circumstances are unknown to reviewers. Researchers and reviewers cannot restrict incentives and study benefits because of concerns that a few individuals might be motivated to pursue these at any cost. The likelihood of any research team being able to impact the structural drivers of HIV risk as they pertain to individual participants during a study is low, but recognition of these factors can increase vigilance and application of the above recommendations to study design and conduct.[6]

Motivators for participation in research trials have been well investigated,[7–13] with what constitutes an undue inducement being debateable.[5 6 10 14 15] The focus is often on financial payments[12 13 15 16] and direct benefits from experimental treatment for the disease under investigation.[8 10 11] A distinction is made between payment to healthy participants and those with the condition under investigation,[8–10 12] as well as between research-naïve and research-experienced populations.[7 8] However, research on inducement has been conducted primarily in high-income countries, including marginalised populations, with limited empirical work in low-and-middle-income countries (LMICs).[10]

Literature on post-trial access research usually focuses on legal and ethical obligations of stakeholders, with some concern for the vulnerability of patients in treatment trials.[17] Post-trial access to effective, safe HIV prevention modalities, has not been considered as possible undue inducement for healthy trial participants who nevertheless have the condition under study, that is, a high risk of HIV acquisition, and thus benefit directly (via access to the modality), and indirectly (via ancillary medical care), while still contributing to the aspirational benefit (to society and future participants).[18] There is a dearth of literature on whether having access to restricted experimental HIV prevention methods encourages sharing and/or selling of experimental prevention products with/to others for financial gain, and whether this creates a further, possibly undue, inducement to consent to participation in HIV prevention post-trial access studies.

This case study illustrates and discusses possible ethical conflicts that may arise for some stakeholders, including trial participants, in LMICs as HIV prevention trials increase in number and access to therapies remain restricted.

BACKGROUND

The Centre for the AIDS Programme of Research in South Africa (CAPRISA) 004 trial demonstrated 39% reduction in acquisition of HIV infection, with 54% reduction in women who used tenofovir gel consistently.[2] The CAPRISA 008 trial which

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followed, was an open-label randomised controlled trial to assess the implementation, effectiveness and safety of 1% tenofovir gel provision through family planning services in KwaZulu-Natal, South Africa.[19] This trial had three main goals:

1. to provide post-trial access to tenofovir gel,
2. to develop and assess an implementation model for pre-exposure prophylaxis (PrEP) provision through family planning services and
3. to collect additional safety data.

The South African Medicines Control Council approved CAPRISA 008 only for consenting, research-experienced CAPRISA 004 participants, who were sexually active, aged 18 years and older, and remained HIV uninfected. The study was conducted at the CAPRISA Vulindlela (rural) and eThekwini (urban) Research Clinics in KwaZulu-Natal, South Africa and their neighbouring family planning clinics. CAPRISA 004 participants consented to be contacted for other trials at the study exit visit and contact numbers were readily available to reach out to volunteers for CAPRISA 008. Of the 786 eligible for CAPRISA 008, 73(9.3%) were not contactable and 716(91.1%) were prescreened; 268(37.4%) were excluded either for reasons of relocation, lack of interest, work/study commitments, HIV seroconversion, failure to return for enrolment, untraceability at last known address, pregnancy or planned pregnancy, death and other reasons. Only 448 (56.9%) were screened with 382 (48.6%) enrolled, with the dropout due to failure to return within the screening window, HIV seroconversion, lack of sexually activity, pregnancy and co-enrolment in another trial. The screening-to-enrolment ratio was 1.7:1. Retention varied between 90% and 100% for all visits throughout the trial.[20] This trial was registered with the South African Department of Health (reference: DOH-27-0812-4129) and ClinicalTrials.gov (reference: NCT01691768) on 5 July 2012. The trial was also approved by the University of KwaZulu-Natal's Biomedical REC (BFC273/010).

CAPRISA 008 was nurse-driven to replicate service in the public sector, with a clinician available for consultation as needed. Inclusion criteria included a negative urine pregnancy test and written agreement to initiate non-barrier contraception at baseline. Urine pregnancy testing was conducted as in CAPRISA 004, with fresh urine samples collected on the day of the visit for point-of-care testing in the clinic. A positive urine pregnancy test during follow-up resulted in cessation of study product until the outcome was confirmed and the urine pregnancy test reverted to negative. Participants remained in follow-up while pregnant. This criterion was the same for the efficacy study,[2] was part of the contraceptive counselling and was agreed to by all participants through the informed consent process. Pelvic examination, including collection of genital samples, was done at enrolment and every 6 months, or more frequently if clinically indicated. Genital samples were stored to assess for markers of safety, risk exposure, product adherence, potential post-trial assessments of activity against sexually transmitted infections (STIs) and tenofovir resistance.[19] Individual tenofovir levels indicative of product adherence were not analysed in real time due to prohibitive costs. Adherence during the study was monitored by clinic and pharmacy staff on an individual participant basis, matching sexual acts to returns of used and unused product applicators.[19]

This case study is of an urban CAPRISA 008 participant, who apparently, driven by personal circumstances, concealed vital clinical information, substituted urine samples for pregnancy testing, underwent trial procedures, received contraception and study drug, potentially compromising her safety and that of her fetus. Although product safety had been established in the 004 study, safety had not been demonstrated in pregnancy.

CASE STUDY SUMMARY

A woman aged 25 years with one previous pregnancy (5 years earlier) was screened early in 2013. At baseline, she perceived herself at low risk of HIV acquisition, based on her in-depth knowledge of her partner and the length of their relationship. The partner was 7 years older than her, and known to be HIV uninfected. She self-reported her date of birth, as her identity document was illegible, and supported this with an affidavit which stated that she was unable to afford a copy of her identity document, due to her indigent status. She reported that she was financially dependent on a child grant, intermittent informal work and variable support from her partner. She reported irregular menses secondary to depot medroxyprogesterone acetate (DMPA) in 2012, with the last menses prior to screening in March 2013. She also reported inconsistent condom use since cessation of DMPA and agreed to restart contraception. A stat dose of DMPA was administered and 20 male condoms dispensed. Clinically, her weight was 54 kg, body mass index was 23.7 and her waist circumference was 79 cm. Urine pregnancy test was negative, with no symptoms or signs on medical history and general physical examination. In the absence of gynaecological symptoms, a pelvic examination was not mandated at the screening visit.

At enrolment she reported a white, inoffensive discharge. Physical examination was repeated and was normal; pelvic examination was reported as 'difficult', with a poorly visualised cervix lying posterolaterally and an offensive, frothy white discharge evident. A urine pregnancy test was not repeated, as the screening test was done less than the protocol mandated 21 days previously. Genital samples were collected as per protocol. Following a review of the visit notes and laboratory results, the clinician provided a script for study product, based on the reported sexual frequency, which amounted to 10 gels for 1 month (a maximum of two gels to be used within 24 hours, coitally based).[2] The discharge was managed syndromically with cefixime, metronidazole and doxycycline as per the then approved South African STI treatment guidelines for non-pregnant patients.[21]

During follow-up the participant was seen monthly at four consecutive visits (relevant findings are reflected in table 1) until visit 4, when marked abdominal distension was noted by the research nurse.

The clinician confirmed the pregnancy on abdominal palpation, noting marked foetal movement, which the participant claimed not to have felt. The initial and repeat urine pregnancy tests were both negative and a blood pregnancy test was requested. Study product was held pending referral for further investigations. The participant denied knowledge of the pregnancy at this stage. An ultrasound and the blood pregnancy test confirmed pregnancy. The participant accepted the diagnosis but continued to deny prior knowledge of the pregnancy. A few months later, she delivered a healthy live male infant via caesarean section, conducted because of a previous caesarean section and for foetal distress secondary to transient neonatal tachypnoea. A bilateral tubal ligation was performed simultaneously at her request. Paediatric assessment at birth revealed no congenital abnormalities. At the study exit, the participant's baby was noted to be normal with no developmental problems.

In tandem, an extensive root cause analysis was conducted by the protocol team, to exclude problems regarding pregnancy test kit integrity and user error. No problems were identified.

Table 1 CAPRISA 008, consecutive monthly clinical parameters for participant, April 2013 to July 2013, eThekwini Clinical Research Site

*Visit/date	Screening	Enrolment	Visit 1.0	Visit 2.0	Visit 3.0	Visit 3.1†	Visit 4.0
Body mass index	23.7	23.7	23.7	24.1	25.0	N/A	26.3
Waist circumference (cm)	79	79	79	79	79	N/A	82
Urine pregnancy test results	Negative	Negative	Negative	Negative	Negative	N/A	Negative
Gels dispensed	N/A	10	20	20	20	20	Product held
Gels returned used	N/A	N/A	10	20	20	20	20
Contraception	DMPA given	N/A	N/A	N/A	DMPA given	N/A	N/A

*Physical and pelvic examinations are symptom directed and not mandated by the protocol at the monthly follow-up visits.
†Interim visit: participant returned to request additional gel as she was going on holiday with her partner.
CAPRISA, Centre for the AIDS Programme of Research in South Africa; DMPA, depot medroxyprogesterone acetate.

However, it was noted that research nurses in HIV prevention were relatively inexperienced in conducting obstetric examinations, did not always conduct bimanual palpation of the uterus and that the method of conducting waist measurement involved only partial disrobing and thus did not facilitate detection of a distended abdomen, especially during winter when bulky clothing is worn.

The clinician requested a private meeting with the participant at the request of the protocol team to discuss the participant's motivation for her decisions and actions and to review the overall health of the baby. The clinician discussed the safety concerns of the protocol team (unknown risks of product use in pregnancy) and invited the participant to describe the thinking behind her decisions. The participant appeared embarrassed and anxious during the discussion and went to great lengths to express her remorse, apologising profusely and disclosing that she knew she was pregnant before she was screened. She then also disclosed substituting her urine samples at clinic visits with samples she had obtained earlier in the day from a person at her home that she knew would be negative. She described taking the urine sample container to the ablution facilities and decanting the sample she brought from home into the container and presenting this to the staff for testing. She said that the pregnancy had been unplanned, and that her partner was angry and threatened infidelity. Consequently, she perceived her risk for HIV acquisition as high and judged ongoing gel usage to be essential to her remaining HIV negative. She resorted to hiding her knowledge of her pregnancy from trial staff, denying symptoms and substituting urine samples. She reported adherence to the gel regimen and that she had not shared gel with anyone else. She was aware of all the risks related to procedures and STI medication but said that her desire to prevent HIV acquisition had overruled these considerations.

Based on the root cause analysis and her disclosure, the participant was counselled and excluded from further participation in the trial, in consultation with CAPRISA's bioethics head, on the grounds that she no longer met inclusion criteria for the study. The case was also reported to the local REC which raised concerns about the site's failure to detect a pregnancy of >12 weeks at screening. The case was also discussed with all clinical project staff to raise awareness, as well as with the Community Research Support Group, who supported the decision to exit the participant from the trial.

DISCUSSION

Among the many possible influences that impact on motivation to participate in clinical trials,[7–13] the desire to access a restricted but proven HIV prevention method, in the light of self-perceived increased risk for HIV acquisition, prompted this participant to misrepresent her true medical status and substitute her urine sample. She was subsequently exposed to products and procedures not approved for use in pregnancy with potential to harm herself and her fetus. The Microbicide Trials Network has since shown a reassuring safety profile for tenofovir gel both in early and late pregnancy,[22] but this information was unavailable at the time.

Devine *et al*[8] hypothesise that compensation may influence willingness to tolerate risk, but that this is more likely in those who participate for financial reward (paid inducement) only. Macklin[14] notes that whether an inducement is considered undue or not, is entirely subjective and based on the individual's value scheme. An empirical assessment of whether moderate payments are undue in clinical trials also concluded that while higher payment motivates participation, there was no evidence that commonly used payments constituted undue inducement. Higher payments, in contrast, have been found to be less influential among poorer participants, but this omits consideration of other factors such as protective benefits and ancillary care.[23] In CAPRISA 008, the National Health Research Ethics Council guideline of 2012 was applied, reimbursing participants fairly for time, travel and inconvenience,[24] which was accepted by the local REC as not undue. The REC however could not anticipate the peculiarities of this participant, whose focus was on access to proven HIV-protective benefits of the study gel through CAPRISA 008, and not a financial incentive. The fact that the participant concealed her pregnancy so actively from the site staff suggests that she knew and understood the study exclusion criteria, and probably other risk information, well, as a result of the consent process and her prior participation in CAPRISA 004. There was no proof that she sold the gel for financial gain.

In studies with the prospect of direct benefit through experimental treatment of a disease, participants motivated solely by financial interests rather than altruism may fabricate symptoms or intentionally self-harm in order to qualify for the study.[8] Participants in HIV prevention efficacy trials do not have a disease per se, but do have high risk for HIV acquisition, and would thus benefit directly from an effective experimental prevention product.[2] In addition, healthy participants are more likely to have financial reward as the primary motivator for participation, especially those with a low monthly income and low education.[12] Notably, all of the women in this trial shared characteristics related to high risk for HIV acquisition, including structural drivers of risk.[1] Some women, when approached, reported pregnancy and refused participation, hence the offer of prevention to mitigate risk alone, cannot be considered undue for this sample in general.

In considering the reasons for this participant's choices, we should take into account her vulnerability to HIV acquisition

due to several possible structural predisposing factors, viz. her poor financial status and consequent dependency on her partner exacerbated by an unplanned pregnancy, the risk of intimate-partner violence, inability to negotiate condom usage, especially during pregnancy and the direct personal benefit of access to HIV prevention and ancillary care. The combination of these factors may potentially have constituted, for this participant, an undue inducement, distinguished here from a paid incentive which does not always equal willingness to accept risk.[14 15] Complicating this further is the variability among volunteers in their willingness to subject themselves to risk.[14] In support of her motivation to access HIV prevention care is data on motivation for joining HIV vaccine efficacy trials: 56% of participants joined to reduce risk and 46% to get protection from HIV, with female participants more motivated to join for the latter.[9] Other factors, such as altruism, financial payments[7–13] cannot be ruled out as coincidental dynamics that were not closely evaluated in this atypical case.

This participant was offered a desirable good (tenofovir gel), as were all participants who enrolled in this post-trial access trial. Her unique circumstances of suspected partner unfaithfulness, poor financial status, perception of increased risk for HIV acquisition and lack of access to effective HIV prevention therapy in the public domain may have made the offer appear excessively good in her specific context and difficult to resist. She concealed her medical status and substituted her urine samples in order to be enrolled, potentially placing her fetus at risk of serious harm through exposure to unapproved procedures and medication.

In our analysis of this case, it is argued that access to the study product did not constitute an undue inducement because inducements typically concern only financial incentives. Her wish to remain protected against HIV was entirely rational and consistent with the overall purpose of the study, even though she violated specific study conditions of which she seems to have been fully aware and took deliberate steps to conceal. Furthermore, product safety had already been partially established by the prior study (CAPRISA 004), but not for pregnancy; this may have influenced her risk assessment. Furthermore, the fact that a single participant engaged in deception to retain access to study product does not necessarily prove that the study team and the REC's appraisal of the incentives and risk/benefit balance was flawed for the study in general.

RECOMMENDATIONS

The case reviewed in this paper supports the following pertinent recommendations:

General:

1. Increase awareness among researchers and staff, RECs and society, of the multiple motivations for participation in post-trial access trials or substudies, and the limitations of REC review.
2. Study benefits may be perceived differently among participants and that focussing on paid inducements and risk/benefit factors is required.

Specific to trial design:

1. Pregnancy testing methods should not rely only on participant sample collection, for example, serum pregnancy testing.
2. Clinician-driven baseline assessments in post-trial access studies should be used to determine eligibility.
3. Weight and height measurements should be conducted in procedure rooms where privacy is guaranteed, rather than in group areas where participants are less inclined to disrobe appropriately.
4. Collection of real-time genital samples should be done to determine exposure to study product when safety concerns arise.
5. Study nurses require advanced training in pregnancy evaluation where pregnancy is an exclusion criterion.

These recommendations should be considered on an individual study level taking into account human and financial resource constraints, length of study visits, study design and the likelihood of the occurrence of similar cases.

CONCLUSION

Women in LMICs are challenged by poor socioeconomic status, gender inequity, high pregnancy rates, increased risk of heterosexual transmission of HIV and variable access to and quality of healthcare. In a region where an increasing number of prevention studies are being conducted, other cases of perceived undue inducement, such as this one, may arise. The risk to safety negates ignoring participant deception in favour of a moral duty that recognises peculiarities in a participant's lived experience. The drive instead should be to rapidly test proven effective products in pregnant women[25] to ensure equitable access to proven therapies even in post-trial access studies. The likelihood of any research team being able to impact the structural drivers of HIV risk as they pertain to individual participants during a study is low, but recognition of these factors can increase vigilance and application of the above recommendations to study design and conduct.

Contributors KTM is the primary author of the paper and worked as the Project Director at the urban site for Centre for the AIDS Programme of Research in South Africa (CAPRISA) 008 and was the overall Safety Officer. JAS has reviewed and provided input to this paper and is the CAPRISA Bioethics Head who reviewed the case and give direction on continued study participation by the participant. LEM is the Principal Investigator of CAPRISA 008, and provided review and input to this paper. DRW has reviewed and made major contributions to this paper based on his expertise in medical ethics.

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