

Payments and Direct Benefits in HIV/AIDS Related Research Projects in Uganda

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Paying research participants in developing countries like Uganda raises ethical concerns over potential for undue inducement. This article, based on an exploratory study, reviewed 49 research protocols from a national HIV/AIDS research ethics committee database. Payments mainly adhered to the reimbursement and compensation payment models. Offers made were diverse but basic in order to limit undue inducement. Implications in terms of undue inducement and possible impact on participants and research are discussed. We end by recommending standardization across comparable studies in the interests of promoting high-quality research, altruism, voluntariness, and restraining unfair reimbursement practices in research.

Keywords: AIDS, HIV, research compensation, Uganda

Uganda's unique health and social problems attract significant local and international research. The number of research projects involving human participants has trebled since 1990 (Uganda National Council for Science and Technology [UNCST], 2007). The HIV/AIDS prevalence in Uganda in particular has attracted significant research interest, including clinical trials and preventive behavioral and observational research. Apart from the high prevalence of HIV/AIDS and novel approaches to its control, interest in conducting HIV/AIDS research in Uganda is also associated with a conducive policy environment, existing research infrastructure, and capacity. Most clinical trials in Uganda focus on HIV/AIDS. The strong association of poverty with the prevalence of HIV/AIDS in Uganda highlights the potential vulnerability of participants to undue inducement, owing to the desire to access health and economic benefits that accrue to many study participants, hence our interest in exploring issues of payments in HIV/AIDS research.

Although much research is potentially beneficial to participants directly, vulnerability of participants to exploitative pressure arising out of reimbursement practices has to be checked.

Uganda, like many other developing countries, has implemented independent ethical review to ensure protection of the rights and welfare of participants. A potentially rigorous institutional framework has been established, coupled with significant capacity-building efforts. Ugandan national guidelines for research involving humans as research participants and guidelines for AIDS vaccine research are referred to, along with a combination of international ethics guidelines such as the Council for International Organizations of Medical Sciences (CIOMS) and World Health Organization (WHO), Helsinki, and Good Clinical Practice Guidelines (Uganda AIDS Commission [UAC], 2006; UNCST, 2007; see also CIOMS, 2002; ICH, 1996; WHO, 2000; World Medical Association, 2008). The instruments, however, are either silent regarding payment or not specific enough (Koen, Slack, Barsdorf & Essack, 2008) and lack specificity regarding appropriate principles and levels of payment relevant to the Ugandan context.

UGANDAN NATIONAL RESEARCH ETHICS GUIDELINES ON REIMBURSEMENTS AND COMPENSATION

According to the Ugandan National guidelines for research (UNCST, 2007), research participants may be reimbursed for lost earnings, travel costs, meals, and other expenses incurred as a result of participating in a study. Participants may also receive free medical services. The guidelines recommend that where direct benefits such as health care are not provided, research participants should be compensated for inconvenience and the time spent away from their work or normal activities. Research participants are not expected to incur costs in order to participate in research. The guidelines also state that research should aim at improving the well-being of research participants and their communities through provision of health care beyond research-related care, optimization of collateral benefits to research communities, provision of good client care during study investigations and procedures, and taking measures to ensure easy access by the community to the test product if proved beneficial.

Payments in Research

Payments in research usually take the form of incentives, reimbursements, compensation, and appreciation rewards (Koen et al., 2008). Incentives differ from compensation and reimbursements (Dickert, 2006; Grady, 2001).

Compensation payments in research involve compensation for the time spent and inconvenience experienced as a result of participating in research. Amounts are determined according to the demands the research places on participants. Reimbursement payments, on the other hand, entail paying participants for direct research-related expenses such as transportation, meals, and babysitting. These are usually calculated on the basis of actual local costs incurred by participants (Wendler, Rackoff, Emanuel, & Grady, 2002). Although reimbursements are easier to determine, compensation for time spent at the research facility and payments for discomfort and inconvenience are more difficult to calculate because they can vary, for instance, with the individual's notion and value of their time (Ndebele, 2006) and is difficult to evaluate objectively (Koen et al., 2008).

Incentive payments are payments, above the actual costs incurred by participants, for purposes of encouraging enrollment. According to Wendler et al. (2002), incentives can be deliberate (added to basic reimbursements) or unintentional (where reimbursements are so attractive as to encourage enrollment). The line, for participants, between payments (in terms of profit making) and compensation for inconvenience is not clear (Hutt, 2003; Ndebele, 2006). In most developing countries, such payments may easily be viewed as incentives because some of the aforementioned compensated items are rarely perceived in terms of money or paid for. The amounts offered could also be high by local standards. Reimbursements and compensations are more common than incentives.

Appreciation payments are bonuses or rewards given to participants after participation in research as a token of appreciation, thanking them for their contribution (Grady, 2005; Wendler et al., 2002).

Payment Models

Forms and approaches to payment of research participants have generated significant debate (see, e.g., Emanuel, 2004; Koen et al., 2008; Lemmens & Elliot, 2003; Wendler et al., 2002). Dickert and Grady (1999) identified several payment models, namely, the market, wage payment, reimbursement, and appreciation models. The market model emphasises payment of incentives for purposes of recruiting research participants with rare conditions or characteristics. It may entail offers of completion bonuses and increase or inflation of incentives to retain participants in trials. Amounts offered are dependent on “demand and supply” forces of the market. Although the model facilitates rapid recruitment and retention of research participants with limited or no financial sacrifices and possibilities of profit making, it has high potential for undue inducement, creation of competition between studies, and commercialization of research participation (Amdur, 2003; Grady, 2005).

The wage payment model entails compensation for time and contribution to research. Amounts are calculated on a standardized hourly wage for hours of participation and inconvenience set according to the unskilled labor market (research is considered unskilled work). The model recognizes contribution of participants, promotes equality in payments, allows for standardization among different studies, and presents less undue inducement risks. A standardized wage may mean undercompensation of some participants while attracting others to whom the amounts may be sufficient (Dickert & Grady 1999; Grady, 2005). Thus, possibilities of problems in recruiting participants across income levels or conversely, a high representation of low-income earners among participants exist. The wage payment may have little impact on recruitment.

The reimbursement model involves payment for actual expenses such as travel and meals, and sometimes time away from work or lost wages. The payments may vary for individual participants. The model precludes profit making, because money is not used to compensate nonfinancial expenses such as effort or discomfort. Amounts paid do not depend on the market. The approach therefore alleviates concerns of undue inducement but also presents challenges for recruitment and does not compensate for personal sacrifice on the part of participants (Amdur, 2003; Dickert & Grady 1999; Grady, 2005).

Under the appreciation model, a range of monetary as well as nonmonetary gifts are offered at the end of the study. This approach has relatively little impact on study recruitment (Dickert & Grady, 1999; Grady, 2005).

Rationale for payments. Depending on their forms, payments may act as inducements if declared to potential participants, and facilitate timely recruitment of adequate numbers and types of participants, particularly for studies that would otherwise have difficulty in recruiting participants. Payments are also a way of showing appreciation, recognition, and respect for research participants' time commitment and their contribution to the social good (Dickert & Grady, 1999; Grady, 2001; Hutt, 2003; Koen et al., 2008; Ndebele, 2006). Participants usually incur direct costs, and the research may offer them little or no potential medical benefits, making it only fair that payments are made (Ndebele, 2006; UNCTST, 2007; Wendler et al., 2002). Nonpayment could imply lack of respect for research participants and injustice if participants incur costs to participate in a study. However, respect for persons also requires the absence of undue influence in the consent process and assurance of justice particularly in terms of fair participant selection (Hutt, 2003). This calls for an exercise in judgment on the part of investigators and of research ethics committees.

As previously mentioned, depending on their form, amount, and timing, payments can act as inducements. Inducements are offers that get people to do things they would not otherwise do. Undue inducements on the other hand are very attractive, excessive, unwarranted, inappropriate, or improper offers of reward or other overtures that lead people to do things to which they would normally have objections, based on risk or on other fundamental values (Emanuel, 2005; Emanuel, Crouch, Arras, Moreno, & Grady, 2003). Undue inducements may lead to inadequate risk–benefit analysis and consequential exposure to unreasonable risks or serious harm. This is particularly possible where the participants attach high value to inducements in contexts of high-risk unethical research. The situation is worse in settings where research ethics committees' (RECs') capacity for risk assessment and general ethical review is weak. Incentives or payments become unethical when they sway decision-making capacities of individuals by making them ignore risks involved in the study (Grady, 2001; Heath, 2001; Hutt, 2003; Ndebele, 2006).

Emanuel (2005) argued that in the absence of elevated risk, payments cannot constitute undue inducement in a competently ethically reviewed study. Offers of goods, no matter how large, cannot constitute undue inducement if the activities are legal, ethical, and prudent, even if they are foolish and entail some risk, as long as the risk is no more than a reasonable person would assume (see also Emanuel, Xolani, & Herman, 2005; Giordano & Harris, 2007).

According to CIOMS (2002), payment made in cash or in kind to research participants should not be so large as to persuade them to take undue risks or volunteer against their better judgment. Children receive special attention with regard to payment, given their potential vulnerability to exploitation. Incentives for children's participation in research are restricted to tokens of appreciation, only to be disclosed at the end of the study. The European Union prohibits incentives or financial inducements altogether (Wendler et al., 2002). Reimbursements for minor direct costs and compensation of an equivalent of a minimum wage for teenagers (in case of missed work) are acceptable in some contexts (Dickert, 2006; Emanuel, 2005; Grady, 2001; Wendler et al., 2002). Similarly, Uganda's ethical guidelines allow tokens of appreciation for child participants, disclosure of which is only permissible at the end of the study. Direct financial and other inducements directed at parents or guardians, and children are disallowed (UNCTST, 2007). A study conducted in the United States revealed that clinical trials involving children are increasing and that payment of child participants, parents, or guardians is becoming common. Amounts paid were mainly determined by the duration of the study and level of engagement per visit. Risk associated with the trials was not a key determinant of payment decisions. Assuming greater risk, in general, should

not be linked to increased payment (Itlis, DeVader, & Matsuo, 2009). Varying payment by risk is likely to increase possibilities of undue inducement. Although it is appropriate for compensation to be directed to the child, desisting from paying younger children directly, especially in cash, is desirable. Payments should not be mentioned or emphasized in the assent process (Wendler et al., 2002). Although incentives for recruitment of child participants are becoming acceptable, a close assessment of their impact on the consent process in developing countries is essential. If incentives are offered after failure to recruit participants, then concerns about undue inducement are heightened.

Challenges. Offers made to research participants have the potential to seriously exert undue influence on individual decisions, thus jeopardizing voluntariness in research (Grady, 2001; Heath, 2001; Hutt, 2003; Ndebele, 2006). Despite awareness, most regulations and guidelines provide little instruction on the calibration of payments (Amdur, 2003; Hutt, 2003). The form, amount, and timing of payment and the socioeconomic and medical status of potential participants usually determine the magnitude of influence; the larger the offer, the greater the potential for distorting judgment or prompting potential participants to provide false information. Compromised voluntariness can also arise after the initial consent. For instance, owing to attractive offers and benefits, research participants may remain in a study despite a possible desire to drop out. Incentives probably have a higher potential for undermining the voluntariness of the informed consent process than other forms of payment (Ndebele, 2006).

In very poor communities, almost any payment over and above precise reimbursements may constitute “undue inducement” to enroll and stay enrolled. In multicenter research in developing countries, owing to high poverty levels, more participants are successfully recruited from developing country sites than from developed countries. This implies that poor or disadvantaged people could be accepting a disproportionate research burden, thus exacerbating inequity. This is even more perturbing given the observation that populations that are susceptible to inducement may be the least able to assess the complex information provided during recruitment and enrollment in order to make an informed decision based on a realistic appreciation of the relative risks and benefits (Dickert, 2006; Emanuel, 2005; Emanuel, Xolani, & Herman, 2005; McNeill, 1997; Ndebele, 2006). On the other hand, these populations are also those most in need of successful products arising out of clinical trials.

In addition to compromising voluntary participation, undue inducements present problems of compromising not only the quality of research but also the well-being of participants through provision of false information by participants or concealing of information that could disqualify them from enrolling or remaining in a study, which in some cases could be detrimental for their health. Cases of fabrication of side effects in order to drop out of trials without loss of payment have been cited (Emanuel, 2004; Grady, 2005; Hutt, 2003). Another case describes participants who coenrolled in two mutually exclusive HIV prevention microbicide studies apparently to receive payments mandated by the South African Medicines Control Council (Center for the AIDS Program of Research in South Africa, 2008). Whereas market-oriented incentives have some benefits for participants, there are possibilities of increasing inequities between rich and poor participants if the poor are paid less and the wealthy are paid more depending on their demands (Lemmens & Elliot, 2003; McNeill, 1997). In support of incentives, there are arguments that there is no substantive evidence that paid studies are more risky than unpaid ones and that if studies fulfill ethical re-

quirements, concerns about the economic distribution of enrolled groups should not arise. However, as noted by Hutt (2003), the possibility of excessive involvement of socioeconomically vulnerable populations in research for administrative or recruitment convenience, remains a valid concern (see also Ashcroft, 2001).

Payments, especially in form of incentives, have the potential of commercializing research participation. In Zimbabwe, reports of refusal to participate in locally sponsored research because of poor incentives, after growing accustomed to generous incentives for participating in internationally sponsored trials, have been cited (Ndebele, 2006; Wendler et al., 2002).

Ethical principles of respect for persons and justice are central in the discussion of compensation and incentives, especially in the context of international collaborative research. Debate concerning associated ethical challenges has generated some responses. RECs in some low-income countries are usually apprehensive of exploitation of their populations (Ndebele, 2006). Such RECs should ensure that research is ethical, taking into consideration issues of collaborative partnerships, social value, scientific validity, fair participant selection, favorable risk–benefit ratio, independent review, informed consent, and ongoing respect for participants (Emanuel, Wendler, Killen, & Grady, 2004). The consent process requires special attention to ensure that participants' consent is informed, rational, and voluntary. Comprehension (especially of known risks) and voluntariness should be assessed. A risk benefit analysis should precede analysis of incentives. Researchers must provide clear, honest information about the study (Emanuel, 2005; McNeill, 1997).

RECs have to ensure that payments are realistic relative to the local economy. To ensure local standardization of payment, research institutions and RECs should develop specific policies or guidelines on how investigators should determine which cases and in what manner participants would be paid. Payment for missed work should be calculated based on the minimum wage (Dickert, 2006; Grady, 2001; Dickert & Grady, 1999; Ndebele, 2006; Wendler et al., 2002). Nondisclosure of payments by researchers has also been proposed. However, it is not deemed ethical by some scholars, because the omission of information from the consent document could be perceived as deceit (Wendler et al., 2002).

Some scholars propose promotion of equity in development through income or resource redistribution, a contentious issue. International health research involving developed and developing countries, and sponsored by developed countries, is an example of this, where there may be significant investment in local research capacity building and infrastructure. It is also suggested that undue inducement be checked by diverting part of the payment intended for individual research participants to benefit wider host communities. Proposed areas of focus include promotion of good health for the benefit of all in the relevant communities, capacity building of local institutions, and technology transfer. It is argued that this could contribute to improving developing countries' capacity to conduct research that directly addresses their own needs and could also be instrumental in protecting locally funded research from unfair international competition for participants.

Given this background, the authors believed that it would be valuable to study, retrospectively, a sample of approved research protocols to determine the types of payment regimes that had been approved, and presumably implemented, in a sample of HIV-related studies in Uganda. Koen et al. (2008), in their review of trial payments in South Africa, recommended that audits be conducted of payment practices, and it is hoped that this study will contribute to this discussion.

METHODS

This article is based on content analysis of secondary data from the UNCST protocol database with specific focus on protocols approved by the HIV Ethics Committee, complemented by key informant interviews. The UNCST HIV Ethics committee is one of the RECs that review HIV/AIDS-related protocols. Other key RECs that review HIV/AIDS protocols (among other research topics) include the Joint Clinical Research Centre and Uganda Virus Research Institute Ethics Committees. The UNCST committee was selected because of its central role in reviewing HIV/AIDS-related protocols and placement at the UNCST, which is mandated to oversee research ethics issues in the country. Protocols from different disciplinary backgrounds, including clinical trials, are reviewed by the committee.

Sample

All HIV/AIDS related protocols within the 6-year period (2000–2005) that were approved and entered into the HIV ethics committee database at the UNCST were reviewed by a UNCST officer with the purpose of extracting consent documents.

Sampling procedure. All approved protocols within the specified period were considered for inclusion. Because the researchers could not access complete protocols, consent documents for the various studies, which should ideally detail essential information of the studies, conditions of participation and offers to research participants, were the main source of information. Sixty-six protocols were considered, 58 of which contained informed consent documents.

Consent documents of the 58 protocols were presented to the researchers by the appointed UNCST staff for analysis. Only 49 (including 7 HIV vaccine trials) had comprehensive information required for analysis. The 49 consent documents were analyzed with the aim of exploring the modes and amounts of reimbursements, compensations, and incentives provided. Some studies included more than one consent form, resulting in more consent forms than studies (see Table 1).

Inclusion and exclusion criteria. The study was restricted to HIV/AIDS-related research (both clinical trials and behavioral studies) submitted to the UNCST HIV Ethics committee. Only research protocols with consent documents were included in the analysis.

Dates applied. The study was carried out in 2005–2006 and the dates of protocols to be reviewed were restricted to the period between 2000 and 2005 to allow the researchers capture current data at the time.

Key informant interviews. These were used to complement secondary data for purposes of triangulation and filling of gaps in our information. Key informants included two members of the HIV Ethics Committee and two staff members of the UNCST knowledgeable in the area of study. Areas of focus included issues of determining the type and amount of payments and informants' experiences or observations concerning the impact of payments on research.

Data analysis. Data extracted from the consent documents were first analyzed using content analysis along the main themes of the study (see Hardon et al., 1994; Varkevisser, Pathmanathan & Brownlee, 2003) as a first step. Descriptive statistics were used because of the relatively small sample size and the data did not reflect a normal distribution, and the chi-square test

TABLE 1
Characteristics of the Studies

<i>Sample Description</i>		<i>Frequency</i>	<i>%</i>
Type of study ^a	Clinical trial	43	87.7
	Behavioral/Other	4	8.2
	Secondary sources	2	4.1
Location ^a	Urban hospital based	45	91.8
	Rural	3	6.1
	Urban and rural	1	2.0
Sponsorship ^a	International	35	71.4
	No indication/Missing	14	28.6
Region of sponsor ^a	United States	26	53.1
	Europe	5	10.2
	Other	1	2.0
Sponsored by pharmaceutical company ^a	No indication/Missing	17	34.7
	Pharmaceutical company sponsored	8	16.3
	No indication/Missing	41	83.7

^a*N* = 49.

was not valid in all attempted cases. Cross-tabulations were used in reporting results, but the tables have been omitted from this article.

Ethical Considerations and Limitations

Authorization for the research was obtained from UNCST. For purposes of confidentiality, the data were extracted by a staff member of UNCST. The authors and titles of the protocols were concealed. One of the main limitations of the analysis is the fact that in the interest of confidentiality, it was not possible to review complete protocols. This limited the exhaustiveness of analysis. Although we were also interested in analyzing the relationship between sponsor details and payment models adopted for the various studies, in some cases, specific details concerning the study sponsors were missing from the consent documents. It is possible that details concerning sponsorship were included elsewhere in the protocols.

RESULTS

Characteristics of the studies reviewed are summarized in Table 1.

The majority of studies were clinical trials (88%), based mainly in urban Kampala, the capital city (92%). Most of the studies were directly or indirectly internationally sponsored. Eight of the studies acknowledged funding from pharmaceutical companies. It was not possible to establish whether funding was obtained from pharmaceutical companies or other research funding agencies for the rest of the studies, as proposals were usually submitted by universities and research institutions. Fifty-three percent of all studies had sponsorship from U.S. sources. Where sponsorship was specified, percentage increased to 81% (26 of 32) of the studies, including 24 of the 29 clini-

cal trials. European sponsorship sources accounted for about 10% (5) of all studies and 16% of studies that specified sources of funding. All 5 were clinical trials (see Table 1).

Payment offers and forms of payment used are summarized in Table 2.

Forms of Payment or Offers

Offers provided were mainly in the form of reimbursements, compensations, and health-related services. These varied by type of research, the duration of engagement per visit, and whether participants participated in the research outside their normal schedule for accessing medical services, which is usually the case with healthy participants. Sixty-one percent (30) of the studies offered reimbursement or compensations. Studies that did not include payment were mostly behavioral studies and studies that used secondary sources or stored materials. Given the intensity of engagement, clinical trials made a variety of offers. For instance, 7% (3) of clinical trials paid for inconvenience, and about 49% (21) offered medical treatment and other health benefits. Vaccine trials, in particular, offered more in terms of amounts paid for reimbursements and compensations than other studies with amounts ranging from 20,000 to 25,000 Ugandan shillings (about US \$14.00; US \$1 = 1,846 Uganda shillings at time of analysis). This is less than the arbitrarily imposed ZAR 150.00 (US \$21.00) required by the South African Medicines Control Council per clinical trial visit in South Africa (Koen et al., 2008). Behavioral studies usually refunded transport expenses.

Reimbursements

Reimbursements to participants were offered by 55% (27) of the 49 studies. Special emphasis was placed on transport and meals, which were offered by 45% (22) and 16% (8) of studies, respectively (see Table 2). Seven of the 8 studies that provided for meals were clinical trials. Meals were paid for in lump sums with other reimbursements. The consent documents did not specify amounts designated for meals. Two studies offered reimbursements for child care where mothers or children were study participants. In the case of HIV research, amounts offered for reimburse-

TABLE 2
Payment/Offer Forms

<i>Aspects of Payment</i>		<i>Frequency</i>	<i>%</i>
Any reimbursement or compensation ^a	Yes	30	61.2
	no	19	38.8
Any reimbursement ^a	Yes	27	55.1
	None or missing	22	44.9
Reimbursement for transport ^a	Yes	22	44.9
	No or missing	27	55.1
Reimbursement for meals ^a	Yes	8	16.3
	no	41	83.7
Reimbursement for missed work or payment for time lost ^a	Yes	8	16.3
	None or missing	41	83.7
Compensation for inconvenience ^a	Yes	3	6.1
	No or missing	46	93.9

^aN = 49.

ments were basic. Where stated (10 studies), reimbursements for transport ranged from 2,000 to 5,000 Ugandan shillings per clinic visit. In other cases, lump sum figures (combining transport, meals, and compensation for inconveniences) were cited. Where indicated, the mean reimbursement was 4,800 shillings, with a mode of 5,000 shillings (approx US\$2.50). Sixteen studies indicated that the amounts would vary according to distance to places of residence. This seems more realistic for research participants but cumbersome for research administrators.

Compensations

Results show that 11 studies (about 22%) compensated research participants for time lost or work missed and inconvenience as a result of their participation (see Table 2). Where specified, the amounts ranged from about 5,000 shillings per visit to 25,000 (for 2 days), with a mean of 14,500 shillings (approx US \$8). Five of the studies did not specify amounts.

Lump Sum Payments

Although other trials differentiated between reimbursements for travel, meals, and compensation for inconveniences, HIV vaccine trials provided a lump sum for every designated clinic visit. Where specified (three of the seven studies), the amounts ranged from about 20,000 to 25,000 Uganda shillings per clinic visit. According to a UNCST informant, the total number of clinic visits for such studies was small. The study that paid an equivalent of 25,000 shillings per visit required only two clinic visits, each requiring overnight stays at the health facility. As noted by Wendler et al. (2002), reimbursement and compensation payments are described and paid per unit of time or procedure and not as lump sums for the total study period.

Appreciation Rewards

Two of the studies adopted a positive strategy of offering tokens of appreciation (such as mosquito nets) at the end of trials.

Incentives

None of the reviewed studies offered incentives as direct payments to prospective participants to facilitate enrollment. Even if payments for inconvenience were regarded by research participants as incentives (Amdur, 2003), such payments were limited. Only three of the studies made such payment.

Form and amount of payment did not vary greatly between studies funded by pharmaceutical companies and those funded by other sources. All but one paid reimbursement for transport. Four of the eight specified that they would not provide benefits other than reimbursements and compensation.

DISCUSSION

Although specific guidelines to determine payments are yet to be developed, offers made to research participants were found to be modest but diverse. In light of Dickert and Grady's (1999)

analysis of payment models, the data suggest that the primary model used was the reimbursement model, where amounts are kept close to the actual costs, followed by the compensation model. Moderation of payments facilitates participant recruitment for studies with limited funding. However, this state of affairs (limiting payments) may have the effect of making Uganda an attractive place for multicenter research, but risks creating an unjust situation for research participants if reimbursements fall below actual participant expenditure.

The practice of reimbursing and compensating research participants for realistic costs incurred per clinical visit or procedure may be effective in limiting undue inducement. Nonspecification of exact amounts provided may also check undue inducement but compromises informed consent. Offering tokens of appreciation at the end of the trial presents minimal challenges of undue inducement. This, however, is subject local value attachment to the token and whether the token is stated in the consent document.

Concerning the possibility of reimbursements and compensations inadvertently acting as incentives if excessive by local standards (Wendler et al., 2002), this study found that offers to research participants in cash, kind, or service forms were modest, given the fact that most of the studies were conducted in urban settings where incomes are higher than in rural areas. A need to convert financial incentives that could result in undue inducement, to community benefits (Ndebele, 2006) did not emerge in these data, as almost all payments were in form only of modest reimbursements and compensations.

In addition to concerns about risk taking and injustice where poor people may shoulder a heavier burden of research, other effects of payments or inducements, such as refusal to participate in research where payments are not made, need to be considered. According to key informant sources and the authors' research experience, nonreimbursed behavioural research is to a large extent still feasible. Recruitment for behavioral studies is comparatively easy, as such research rarely involves more than minimal risk. However, evidence of interest in financial gains is emerging among communities exposed to research (Dickert, 2006). Similar to Ndebele's (2006) observation in Zimbabwe, it is becoming increasingly difficult to recruit participants in some Ugandan urban communities. Apart from possible "research fatigue" and lack of time, refusals also appear to be associated with the fact that prospective research participants increasingly appear to expect reimbursements or compensations irrespective of the type of research in question. The potential for commercialization of research participation in the Ugandan context also exists; a study carried out in a rural part of the country revealed that a significant proportion of potential participants desired compensations in monetary form (Dickert, 2006).

Whereas reimbursement for costs incurred by participants is acceptable, equating participation in research to work, based on a wage payment model (Dickert, 2006; Emanuel, 2004, 2005), is more ethically complex. Work and wages should be used only as a basis for calculation of compensation time lost or work forfeited as a result of participating in a study (which should be a flat rate) and should not be fronted to participants as an earning. The actual value of their participation could be of higher than the fronted "unskilled work" (see also Amdur, 2003). In addition, according to McNeill (1997), work is not an appropriate analogy for participating in research, because the actual magnitude of risk of harm is not known (in advance) as is the case for most kinds of work. This approach encourages commercialization of participation in research as appears to be widespread in the United States.

In Uganda, it seems desirable that approaches to payment are contextually appropriate and culturally relevant. Making participants incur costs to participate in research is unethical (UAC,

2006). In case of extra offers over and above reimbursement (where necessary), the appreciation model should be adopted. Appreciation rewards should be provided at the end of the study and not earlier, even when planned in advance. Such an approach, if modest and approved by RECs, would pose limited risk of undue inducement.

According to key informants, all payments are principally negotiated by RECs and investigators. In contrast, the Medicines Control Council in South Africa has stipulated a mandatory payment of ZAR 150.00 (US \$21.00) per clinical trial visit (Koen et al., 2008). No mandatory payment exists, however, for other types of studies. In a low-income country like Uganda, whereas aspiration for equity (concerning such offers) in multicenter research is desirable, according to a UNCST informant, RECs are, hopefully, vigilant about checking undue inducement, especially where studies involve more than minimal risk. Emphasis is therefore placed on limiting payments. As noted by Lemmens and Elliot (2003), some observers expect participation in research to be based solely on altruism. Research participants are not expected to negotiate payment because payments are not supposed to be the main focus of their involvement. It is assumed that their interests are addressed by community representatives on RECs. According to a UNCST informant, Uganda views (HIV/AIDS) research as a partnership that not only facilitates local capacity building/technological transfer but also contributes to promotion of international relations. This could lead to the restraint of generous reimbursements so that Uganda is not perceived as an expensive international research site. On the other hand, this policy could be an injustice to research participants.

Optimization of collateral benefits to research communities is encouraged. The Uganda Guidelines for AIDS Vaccine Research (UAC, 2006) encourage provision of community benefits, especially improvement of health service infrastructure for the benefit of the wider community. This is not mandatory, however. Uganda has not independently initiated any locally funded clinical trials comparable in scope to HIV vaccine trials. According to a key informant, locally funded health studies are mainly behavioral in nature, or based on secondary data or already-collected samples.

There are concerns over possible exploitation of developing countries by for-profit pharmaceutical companies, by taking advantage of low socioeconomic status, inadequate protection of human rights, and inadequate understanding of scientific research in such countries to minimize research costs, thereby optimizing profits. Gaps that exist in equitable access to research resources—for instance, payments, collateral benefits, and trial products if proved effective especially in multicenter research—require attention. The differences in contextual economic statuses and ethical concerns of undue inducement are appreciated. However, in the interest of equity in resource investment in research, and a fair share in participation in research, investments in the research process in terms of payments should be comparable. Research does not always result in effective products, and even when it does, reasonable access to trial products is rare owing to weak negotiation and inadequate monitoring capacity. These make this approach unfair.

Researched communities in Uganda could be defined as a vulnerable. Although it is possible that many of the clinical trials could have been funded by pharmaceutical companies, according to a key informant, many operate through university institutions and the trial drugs are often portrayed as donations to the respective university institutions in sponsoring countries. This makes it seem unreasonable to insist on reasonable access to trial products. Although the country in general benefits if pharmaceutical companies contribute to resources for making regular vaccines available (free of charge), issues of equitable sharing of responsibilities and benefits require rethinking.

Ensuring adequate independent evaluation of research protocols is of paramount importance (Emanuel, 2005). RECs should have the capacity to negotiate and make informed and principled decisions on reimbursements, compensation, individual incentives, and community benefits for their participants. This requires capacity building for RECs (Milford, Wassenaar, & Slack, 2006).

The form, amount, and timing of disbursement payments requires critical review. The rationale for payments should be included in consent documents. Local standardization of payment is essential in checking competition and unwanted creation of barriers to future studies with limited funding. As recommended by some (Koen et al., 2008; Ndebele, 2006), setting of standardized local and international levels of payment rates for both local and international research is essential. These rates should be based on time, inconvenience, and expenses (Koen et al., 2008). Some approaches to payment that limit undue inducement include avoiding lump sum payments that make amounts appear excessive, deferring payments, and offering of noncash payments.

Because participation in research in our view should not be equated to paid manual labor, reference to the minimum wage should only be used as a basis for determining compensations for lost work. Unfortunately, the minimum wage in Uganda is yet to be officially determined. Until the minimum wage is determined, compensations should be contextually determined in consultation with community representatives on RECs and should be calculated proportionate to duration of engagement. If the daily minimum wage, for instance, is 8,000 shillings for 8 hr, then each hour of involvement should be worth 1,000 shillings. Other reimbursements should be determined as close to actual cost as possible. This approach would limit possibilities of undue inducement. Extra resources should be channeled toward community benefits. As noted by Iltis et al. (2006), compensations should not increase with increases in risk. For research that entails more than minimal risk, instead of significant increments in recruitment incentives, provision for comprehensive insurance of participants should be made.

CONCLUDING REMARKS

Payments for HIV/AIDS research in Uganda were found to be modest, at least in comparison to known requirements in South Africa. As such there is the possible risk of exploitation rather than the risk of undue inducement. However, standardization and development of contextually relevant guidelines for the various types of offers appear to be necessary if both exploitation and undue inducement are to be avoided.

Concerning levels of payment, a well-defined fair approach to determining levels of reimbursement, compensations, and other offers is essential. Guidelines should be developed through interstakeholder participatory processes. There should be some negotiable parameters by relevant stakeholders within a defined framework. Justification of levels of payments by researchers and ethics committees in light of possible impacts is essential.

To facilitate development of guidelines concerning payments, further research on the following issues is recommended:

- The impact of various forms of payments or offers on recruitment and retention of participants
- The extent to which such offers constrain recruitment for low-budget research in poor communities

- The effect of the various offers on the quality of research participants' voluntary informed consent
- Establishment of socioeconomic characteristics of trial participants in both paid and unpaid studies with the aim of ascertaining whether disproportionate numbers of vulnerable participants are recruited
- How key research stakeholders view payments. Such stakeholders should include trial participants, members of RECs, researchers, regulators, and members of Community Advisory Boards

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REFERENCES

- Amdur, R. (2003). *Institutional review board member handbook*. Boston: Jones and Bartlett.
- Ashcroft, R. E. (2001). Money, consent, and exploitation in research. *American Journal of Bioethics* 1(2), 62–63.
- Center for the AIDS Program of Research in South Africa. (2008, April). Inadvertent enrollment of ineligible participants in CAPRISA 004. *CAPRISA Newsletter* 7(4), 2. Retrieved May 8, 2009, from <http://www.caprisa.org/Newsletters/2008April.pdf>
- Council for International Organizations of Medical Sciences. (2002). *International ethical guidelines for biomedical research involving human subjects*. Geneva, Switzerland: CIOMS.
- Dickert, N. (2006). *Coercion and undue inducement in research: Money and other offers*. Baltimore: Johns Hopkins School of Medicine and Bloomberg School of Public Health. Retrieved August 21, 2007, from <http://ocw.jhsph.edu/courses/EthicsHumanSubjectResearch/PDFs/Coercion.pdf>
- Dickert, N., & Grady C. (1999). What's the price of a research subject? Approaches to payment for research participation. *New England Journal of Medicine*, 341, 198–203.
- Emanuel, E. (2004). Ending concerns about undue inducement. *Journal of Law, Medicine & Ethics*, 32(1), 100–105.
- Emanuel, E. (2005). Undue inducement: Nonsense on stilts? *American Journal of Bioethics*, 5(5), 9–13
- Emanuel, E., Crouch, R., Arras, J., Moreno, J., & Grady, C. (2003). The Belmont Report: Ethical principles and guidelines for the protection of human subjects of research. In E. Emanuel, R. A. Crouch, J. D. Arras, J. D. Moreno, & C. Grady (Eds.), *Ethical and regulatory aspects of clinical research: Readings and commentary* (pp. 33–38). Baltimore: Johns Hopkins Press.
- Emanuel, E., Xolani, E. C., & Herman A. (2005). Undue inducement in clinical research in developing countries: Is it a worry? *Lancet*, 336, 336–340.
- Emanuel, E., Wendler, D., Killen, J., & Grady, C. (2004). What makes clinical trials in developing countries ethical? *Journal of Infectious Diseases*, 189, 930–937.

- Giordano, S., & Harris, J. (2007). Ethics and research on human genetic material. In J. V. Lavery, C. Grady, E. R. Wahl, & E. J. Emanuel (Eds.), *Ethical issues in international biomedical research: A casebook* (pp. 174–180). New York: Oxford University Press
- Grady, C. (2001). Money for research participation: Does it jeopardize informed consent? *American Journal of Bioethics*, 1(2), 40–44.
- Grady, C. (2005). Payment of clinical research subjects. *Journal of Clinical Investigation*, 115(7), 1681–1687.
- Hardon, A., Boonmongkon, P., Streefland, P., Lim Tan, M., Hongvivatana, T., Geest, S. V. D., et al. (1994). *Applied health research manual: Anthropology of health and health care*. Amsterdam: Het Spinhuis.
- Heath, E. (2001). On considering (what I might do for) money. *American Journal of Bioethics*, 1(2), 63–64.
- Hutt, L. E. (2003). Paying research subjects: Historical considerations. *Health Law Institute*. 12(1), 16–20. Retrieved July 23, 2007, from http://www.law.ualberta.ca/centres/hli/pdfs/hlr/v12_1/03_Hutt.pdf
- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. (1996). *ICH harmonized tripartite guideline: Guideline for good clinical practice, ICH*. Retrieved May 13, 2009, from <http://www.ich.org/cache/compo/475-272-1.html#E8>
- Iltis, A. S., DeVader, S., & Matsuo, H. (2006). Payments to children and adolescents enrolled in research: A pilot study. *Pediatrics*, 118, 1546–1552.
- Koen, J., Slack, C., Barsdorf, N., & Essack, Z. (2008). Payment of trial participants can be ethically sound: Moving past a flat rate. *South African Medical Journal*, 98, 926–929.
- Lemmens, T., & Elliot, C. (2003). Justice for the professional guinea pig. In E. Emanuel, R. Crouch, J. Arras, J. Moreno, & C. Grady (Eds.), *Ethical and regulatory aspects of clinical research: Readings and commentary* (pp. 183–184). Baltimore: Johns Hopkins Press.
- McNeill, P. (1997). A response to Wilkinson and Moore: Paying people to participate in research: Why not? *Bioethics*, 11, 390–396.
- Milford, C., Wassenaar, D. R., & Slack, C. M. (2006). Perceived capacity of selected African research ethics committees to review HIV vaccine trial protocols. *IRB*, 28(2), 1–9.
- Ndebele, P. (2006). Undue inducement in internationally sponsored research. *Medical Humanities Report*, 27(2). Retrieved August 21, 2007, from <http://www.bioethics.msu.edu/mhr/06w/Undue%20Inducement.htm>
- Uganda AIDS Commission (2006). *Uganda guidelines for aids vaccine research: A guide for vaccine research, development and evaluation*, Kampala: Uganda AIDS Commission, European Union and the Uganda HIV/AIDS Partnership.
- Uganda National Council for Science and Technology. (2007). *National guidelines for research involving humans as research participants: Uganda*. Kampala: Uganda National Council for Science and Technology.
- Varkevisser, C. M., Pathmanathan, I., & Brownlee, A. (2003). *Designing and conducting health system research projects* (Vol. 1). Amsterdam: KIT Publishers in association with IDRC and WHO.
- Wendler, D., Rackoff, J., Emanuel, E., & Grady, C. (2002). The ethics of paying for children's participation in research. *Journal of Pediatrics*, 141(2), 166–171.
- World Health Organization. (2000). *Operational guidelines for ethical committees that review biomedical research*. Geneva, Switzerland: Author.
- World Medical Association. (2008). *Declaration of Helsinki: Ethical principles for medical research involving human subjects* [1964]. Ferney-Voltaire, France: Author. Retrieved May 13, 2009, from <http://www.wma.net/e/policy/pdf/17c.pdf>

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