Payment of clinical trial participants

The payment of clinical trial participants is contentious, particularly within a developing world context. The dividing line between 'fair compensation' and 'undue inducement' is difficult to determine. Two years ago, the *Sunday Times* highlighted this issue and sparked considerable debate in their article 'Girls bunk school to cash in on HIV trials: School kids offered money to test gel product each time they have sex'. (This was a microbicide gel HIV prevention study.) The 'cash' given to study participants was the Medicines Control Council (MCC) R150.00 travel reimbursement requirement for all South African clinical trial participants, irrespective of the clinical nature and context of the study. This somewhat infamous sum of R150 was hotly debated in research ethics committees around the country, and became a bone of contention between sponsors (who wished to comply with the MCC and get on with the trial) and ethics committees who often regarded the amount as inappropriate and amounting to 'undue inducement'. Recently, the MCC appears to be more flexible in the application of this rule; however, its legacy still holds sway.

Burgess, Sulzer and Emanuel (published in this issue of the *SAMJ*)[1] investigated patients' perspectives on clinical trial participation and the issue of payment. Their patients were from a low- to middle-income peri-urban group, with 60% able to attend study visits using a private car. The majority of participants felt that they should be reimbursed for travel costs. However, most participants believed that the R150 did not influence them to distort information in order to gain admission to the study, and most participants stated that they would have participated anyway, even if no payment were offered. Their study provides valuable insights into this ongoing debate, and needs to be repeated across the country. The opinion by participants that they should at least be paid for travel expenses is echoed internationally.[2]

Clarifying what the concept of 'participant remuneration' means for a particular clinical trial is important. Does it mean payment for expenses such as travel and meals; payment for time, inconvenience and recognition of effort; or overt inducement?[2] When, if ever, is each category of reimbursement appropriate, or when does it amount to covert inducement? Payment for expenses incurred seems to be generally accepted. However, payment for time, inconvenience and recognition of a contribution is far more contentious, and it is more difficult to quantify what monetary value would be appropriate. The third category of payment, i.e. an inducement to participate, is widely regarded by the South African research ethics committee fraternity as not acceptable, because it may influence and undermine a participant's autonomy and ability to consent freely to participation. This is particularly important when a study involves more than minimal risk, or a risk/benefit ratio that is equivocal. I suggest that there may be occasions when some form of overt inducement, monetary or otherwise, may be appropriate.

The spectrum of clinical trials conducted in South Africa is extensive and includes industry-sponsored trials and investigator-initiated, grant-funded research. Clinical trial sites occur across the spectrum of health care in South Africa. Trial participants, too, range from the more affluent users of private health care facilities, to impoverished rural and peri-urban communities. This debate is often assumed to apply largely to industry-sponsored clinical trials and their spectrum of participants. However, any blanket decision by a regulatory authority regarding payment to participants applies to all clinical trials, including grant-funded studies that address important public health care issues such as HIV and TB. The value and meaning for an executive of a R150 payment to participate in a study differs completely from that of an unemployed, single mother living in a rural area for similar participation. The fact that R150 is almost equivalent to the monthly government childcare subsidy highlights this discrepancy.

The demographic characteristics of participants and the nature of clinical trials vary widely. Some trials are relatively low risk with good prospects of directly benefiting the participant. Others are higher risk, and yet others may have little prospect of direct benefit although they may contribute to knowledge or the common good. These factors must be taken into consideration when deciding whether or not some form of payment should be made to clinical trial participants. Another issue that should be considered is the notion of the 'therapeutic misconception' – the idea that many trial participants do not distinguish clearly between medical treatment and research. Appropriate payment of trial participants in such situations may reduce the 'therapeutic misconception' and increase participant autonomy.[3]

The MCC 'R150 rule' applies to investigator-driven grant-funded research and industry-sponsored research. These studies often address very important public health care issues that are sometimes ignored by the pharmaceutical industry. They are funded by government institutions and foundations, often on shoe-string budgets. A recent study conducted in a tertiary academic hospital involving patients receiving chronic haemodialysis almost had to be abandoned because of the MCC's insistence on the universal application of the 'R150 rule', which added a further R48 000 to the limited study budget. A trial enrolling 300 participants over a period of 2 years, with 10 study visits per participant, would require an extra R450 000 just to remunerate participants. While the reimbursement of actual travel costs and meals is an accepted

norm, important non-industry-sponsored research may go unfunded if there is no 'negotiating space' to determine fair reimbursement of the study-related costs incurred by participants.

A flip side to the above argument is minimal-risk research that may potentially have significant positive public health impact and influence policy. In such circumstances, a payment specifically to induce participation may be warranted, and would need to be evaluated case by case. This controversial assertion will almost certainly be challenged. However, consider the large-cluster randomised TB chemoprophylaxis study currently being conducted in the South African mining industry.[4] This study is investigating the impact, at community level, on the prevalence rates of tuberculosis in miners, when INH chemoprophylaxis is administered to the employees of entire mine shafts. As the HIV-tuberculosis epidemic is devastating communities across sub-Saharan Africa, such a study has the potential to radically change policy and save lives. However, for it to be successful, a high recruitment rate per shaft is essential. Failure to achieve almost complete coverage may jeopardise study outcomes and result in a waste of valuable resources and opportunity. Currently, the ethically approved recruitment strategy involves offering small gift incentives, such as a cap or T-shirt, at intervals over the course of the study. The total combined monetary value of these incentives per participant is about R150.00. However, such a study (where high levels of community participation are critical for the integrity of the study) may present an opportunity to re-examine entrenched ethical norms related to payment for the purposes of covert inducement to participate and remain in the study. The development of trial site community advisory boards may be invaluable in assisting researchers and ethics committees to determine what sort of remuneration is appropriate for a given set of clinical trial- and participant-related circumstances.[5]

In conclusion, a one-size-fits-all approach to payment of clinical trial participants is injudicious. Whether or not any form of payment should be offered to participants is contingent on many factors, such as the nature of the study, degree of risk involved, profile of participants, funding source, and issues related to the potential public health implications of the study. Participant remuneration should be evaluated on a study-by-study basis. The principal investigator and sponsor should discuss participant remuneration in the protocol. However, the final decision should be made, after careful consideration of all factors, by the research ethics committee that reviews and approves the study.

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