Clinical trial remuneration: the patients' perspective

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To the Editor: The remuneration of patients in clinical trials is controversial because money may influence their decision to participate. When the amount becomes irresistible, it represents undue inducement and may persuade patients to participate in a clinical trial or resist discontinuation against their better judgement, which can potentially compromise the informed consent process and the scientific validity of the trial.[1] This is particularly relevant in South Africa, where the potential to exploit vulnerable communities readily exists.[2]

The task of creating guidelines to assist the clinical trial industry in deciding what remuneration, if any, trial patients should receive is fraught with complexities. Regulatory authorities provide general recommendations cautioning against undue inducement, but no guidance on when money is not due, or how much money constitutes undue inducement.[1] The Council for International Organisations of Medical Sciences (CIOMS) gives the most comprehensive guideline, stating that ' … subjects may be paid for inconvenience and time spent and should be reimbursed for expenses incurred, in connection with their participation in research'.[1,3] South Africa's Medicines Control Council (MCC) stipulates that all Phase II - IV clinical trial participants receive R150 per study visit – which has been much criticised by the local research community.

Methods

Our study aimed to (*i*) document the opinions of trial participants regarding remuneration in clinical trials, and (*ii*) clarify the amount of money that would represent an undue inducement to a South African clinical trial patient.

The study was conducted by TREAD Research, a clinical trial unit located within Tygerberg Hospital, Parow. Patients attending the unit between January 2005 and May 2006 were approached to participate. The study was approved by Stellenbosch University's Ethics Committee. Consenting patients completed an anonymous validated questionnaire in their home language. Patients were assigned a random consecutive number, and no identifying data were recorded on the questionnaire. Patients were asked to provide basic demographic data, level of completed school education, current occupation, monthly earnings, health care system used (state or private) and method of transport to the study visits. Patients were also asked questions regarding their remuneration and for what purpose they used it. Data were entered into a spreadsheet programme by an independent data capturer. All data were analysed by means of Statistica Software Version 7.0 (© StatSoft, Inc., USA).

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Results

A total of 250 patients completed the questionnaire. The mean (±SD) age of subjects was 56.3 ±10.9 years. The majority of the respondents were Afrikaans (71.7%). There were 118 male subjects (47.0%) and 132 female subjects (52.6%). Unemployed respondents comprised 66.5%, with only 31.5% registering a paying job. The median (lower; upper quartile) monthly family income was R1 800 (R740; R5 200). Of the respondents, 34.0% had completed grade 12 (Matric), 40.6% received after school training, and 12.4% had a university education. Sixty-four per cent were solely dependent on the public heath care system, 15.1% had private health care, and 18.7% made use of both public and private heath care. Modes of transport to the clinic were private car (60.7%), taxi (25.6%), train (7.2%) and bus (6.5%).

Seventy-four per cent of trial participants felt that they should receive payment for their clinic visits, yet 93.6% indicated that they would still participate in a clinical trial if they received *no* payment. Ninety-four per cent indicated that they would *not* hide details regarding their medical history in order to participate in a trial. The amount of R150 would **not** tempt 90.0% of participants to withhold information about their true state of health in order to participate in a study. Ninety-one per cent indicated that payment was not used by the investigator as encouragement to participate in a clinical trial.

Regarding why they felt they should be paid for participating in a clinical trial, 72.9% responded that payment should be made to cover travel expenses, 13.9% that it was an incentive to participate, and 13.1% that it covered time spent (Fig. 1). Regarding their use of the remuneration, 88.8% of subjects reported using it for travel expenses, 7.2% for nothing specific, and 6.4% for necessities (Fig. 2).

Of this study population, 64.1% depended solely on the state health care system. Only 34.0% had completed grade 12, and 66.5% were unemployed. Despite these facts, most respondents (93.6%) indicated that they would still participate in a clinical trial if they received *no* payment.

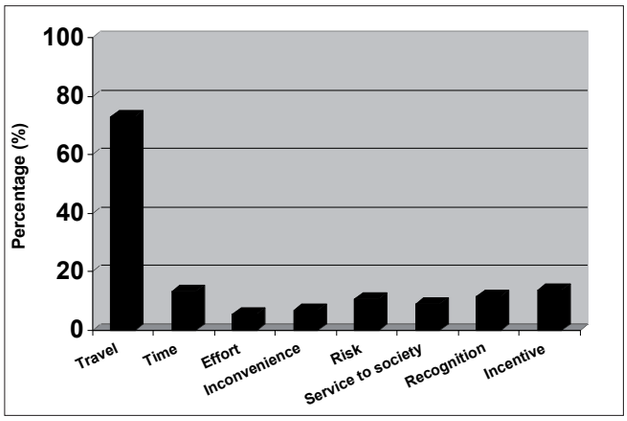

Fig. 1. Subjects' responses to why they felt that they should be paid (N=194), presented as a percentage of total respondents.

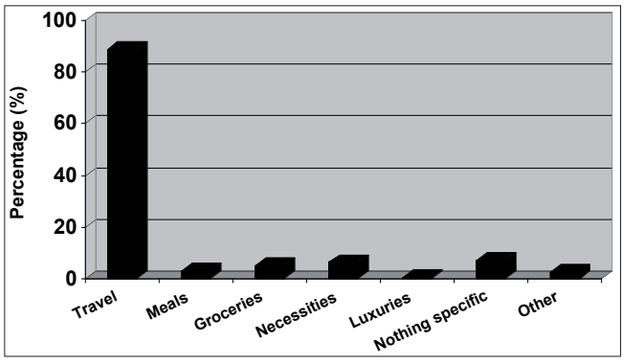

Fig. 2. Subjects' responses to what they use their remuneration for (N=286), presented as a percentage of total respondents.

Discussion

The most common reasons for our patients participating in clinical trials included contributing to scientific understanding, learning about their condition, achieving a sense of belonging, and having access to services that they would otherwise be unable to afford (Burgess *et al.*, unpublished data). In addition, 80% of respondents did *not* think clinical trial participation was an easy way to obtain money.

Our study revealed that trial participants believed that they should receive remuneration to compensate for travel expenses and time spent (Fig. 1). The majority of respondents used the remuneration to cover transport costs (Fig. 2). This echoes the CIOMS guidelines.[3]

Blanket compensation, such as that mandated by the MCC, is contentious in light of these findings as it does not consider the complexities of the clinical trial setting. These include the phase and design of the study, disease under study, study subject and the fact that money means different things to different people. A phase I study, where healthy volunteers often undergo repeated phlebotomy and exposure to highly experimental treatments, cannot be compared with a phase IV post-marketing study. A patient suffering from a life-threatening condition may make health decisions based on different criteria to the otherwise well patient with mild seasonal asthma. In making decisions on matters of health, wealthy employed participants with medical insurance are unlikely to use the same criteria as poorly educated, unemployed participants, who are reliant on state health care. Finally, although many may agree that money represents an inducement, it is not clear what amount of money constitutes *undue* inducement.[1]

How the MCC reached their decision that trial participants receive R150 per study visit is unclear. However, it is necesssary to contextualise this amount of money to understand what it means to a trial participant in this country. The average study visit takes approximately 2 hours, which effectively means that clinical trial patients receive R75 per hour for their participation. However, the average South African salary is currently R51 per hour.[4] The median (first, third quartile) hourly income of these study participants was R10.23 (R4.10, R29.54).

These figures highlight the potential for undue inducement. Most guidelines simply caution against 'undue inducement' but do not describe when or how much money constitutes undue inducement. The *Belmont Report* states that '… undue influence occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance'.[5] The majority of respondents in the present study indicated that they would not hide details regarding their medical history to qualify for a trial, and that the amount of R150 would not tempt them to withhold information about their true state of health. Furthermore, according to these respondents, investigators did not use payment to encourage trial participation.

These results therefore suggest that R150 does not constitute an undue inducement as it does not compromise participants' integrity or freedom of choice and ability to give *voluntary* consent. However, in the South African context of an average hourly salary of R51, the amount of R150 may be considered an '… excessive and unwarranted reward', as cautioned against.[5] We also found that the majority of trial participants were of the opinion that remuneration should be provided for travel expenses and time spent at the study visit. This contradicts the concept of a blanket compensation rate for trial participation and also questions for what purpose patients in this country are remunerated.

Generalisations regarding trial reimbursement for clinical trial participation are clearly impossible. This study indicates that remuneration should be calculated individually for travel expenses and time. Instead of stipulating their generalised and ostensibly unjustifiable remuneration fee, the regulatory authority could offer a written policy guideline advocating the purpose and intention of clinical trial remuneration. Clinical trialists could then customise this policy on an individualised, per patient basis. The challenge remains to find a remuneration figure which is not excessive and thereby does not constitute

undue inducement, while at the same time protecting against exploitation of vulnerable communities who are involved in clinical research in this country.

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Falsely elevated plasma creatinine levels as a marker of nitromethane poisoning

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To the Editor: We report 6 cases of accidental nitromethane poisoning, of which there are only 4 reported cases in the world literature. The significance of this poisoning is that nitromethane interacts with the widely used Jaffe reaction method of determining plasma creatinine values. The enzymatic creatinine assay method and cystatin C determinations are not yet widely available in South African laboratories. The resulting, falsely elevated plasma creatinine values, which can be very high, can be misinterpreted by clinicians as a marker of severe renal failure and could lead to inappropriate management. We also report the first known death following nitromethane ingestion-induced status epilepticus.

Case report

Six homeless people presented at a regional hospital in the Western Cape. They had all ingested unknown quantities of the liquid contents of a discarded wine bottle.

The index patient was a 34-year-old man who presented to the emergency department having suffered three generalised tonic-clonic seizures. He had a Glasgow Coma Score of 9/15, blood pressure 110/70 mmHg, pulse rate 62/min, respiratory rate 24/min, finger-prick glucose test 13 mmol/l and oxygen saturation 94% on room air. He was markedly agitated and initially displayed paranoid delusions. He had status epilepticus and was treated with intravenous diazepam (a total of 40 mg in 12 hours), phenytoin 1 500 mg and later phenobarbitone 1 000 mg. Failing to respond to treatment, he was transferred to the intensive care unit (ICU) of the central hospital for ventilation. Co-amoxiclav was prescribed for possible aspiration pneumonia, and he was maintained on a diazepam infusion for the convulsions. Later he required inotropic support for haemodynamic instability and a thiopentone infusion for control of seizures. A lumbar puncture and contrasted computed tomography (CT) scan showed no abnormalities. His urine output remained more than 1 ml/kg/h during admission. He deteriorated progressively, developed diabetes insipidus, and was declared brain-dead 11 days later.

Initial arterial blood gas analysis revealed methaemoglobinaemia (blood methaemoglobin level 2.6 g/dl) with arterial saturation of 95% on FiO_2 40%; blood results were plasma Na 137 mmol/l, plasma K 4.4 mmol/l, plasma urea 8.6 mmol/l, and plasma creatinine 10 122 µmol/l. The spontaneous decrease in plasma creatinine levels of the index patient is shown in Fig. 1.

The 5 other intoxicated patients all suffered severe visual hallucinations and paranoid delusions upon admission but their clinical examinations and vital signs were all normal. Each patient received saline infusions of 100 ml/h to maintain an adequate urine output of more than 1 ml/kg/h. They also received haloperidol 10 mg and clonazepam 2 mg with minimal effect on their mental status. Three of these patients had a single tonic-clonic seizure each, responding well to intravenous diazepam. All the patients received a loading dose of phenytoin of 1 500 mg. The psychotic symptoms dissipated by day 3. These patients' presenting creatinine values were 6 377 µmol/l, 3 531 µmol/l, 2 971 µmol/l, 3 212 µmol/l, and

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