Should healthy volunteers in clinical trials be paid according to risk?

Eleri Jones and **Kathleen Liddell** argue that objections to paying according to risk are paternalistic, but **John Saunders** thinks that it would lead to people being exposed to unacceptable danger

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Competing interests: None declared.

YES The severe reactions experienced by healthy volunteers in the TGN1412 (Northwick Park) trial have led to questions about payment for participation.[1] Currently, the dominant view is that only time and expenses should be remunerated. By this logic a healthy volunteer participating in a half day trial at risk of immunological storm is paid the same as a volunteer participating in a half day observational study. This is objectionable for two reasons: firstly, because there should be recognition of a volunteer's gift to society[2] for the higher risks in some trials and, secondly, because it is inconsistent with other practices in society.

The law and current guidelines

The law allows volunteers to be paid subject to approval by a research ethics committee.[3] In addition, the volunteer must give free and informed consent, yet there has been little judicial guidance on the influences, such as money, that render a competent person's decision involuntary. In medical treatment cases, the influence must be more than just persuasive.[4 5] In financial cases, independent advice is a central consideration.[6] Neither line of authority necessarily applies to medical research.

Guidelines for clinical trials are often vague, stating that proposed payments should not be so high as to cause coercion or undue influence. The Association of the British Pharmaceutical Industry states that "Payment must never be related to risk,"[7] whereas the Royal College of Physicians notes that "Payments may be variably made for time, inconvenience, travel, or incurring risk."[8] Importantly, payment according to risk does not mean the riskiness of the trial is open-ended. In addition to the individual's agreement, the level of risk must comply with the limits in the clinical trial directive and be approved by an ethics committee.

Why pay more?

Healthy volunteers who agree to participate in a clinical trial do so on the understanding that there is no personal benefit but a risk of adverse reactions. Some agree to undertake

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Competing interests: JS is a research ethics adviser for the National Research Ethics Service.

NO Many years ago, I read a popular book on astronomy for young people in which the author suggested that the first person to be launched into orbit around the moon would be a volunteer with no prospect of returning to earth. His place in history would be assured and he would have sacrificed his life for information of inestimable scientific value. I can't remember if payment was suggested, but I recall my childish reaction to the proposal—surely this couldn't be done. There are certain things that research participants should not be asked to do, no matter how important.

Undoubtedly some questions are important and seemingly of pressing urgency: the limits of human endurance to new chemical agents or biological weapons in wartime, for example. But such high risk investigations are not justifiable. Treating humans merely as a means to further knowledge dehumanises the experimental subject, no matter how informed the consent. Where risk is high, people should not knowingly be exposed to it. As Jonas said, "Progress is an optional goal, not an unconditional commitment" and "a slower progress in the conquest of disease would not threaten society."[1]

The first objection to paying healthy human volunteers to participate in phase I trials on the basis of risk is therefore that the level of risk should not be so high as to necessitate such payment in the first place. High risk studies should not be carried out. As Royal College of Physicians guidelines state: "it should not be necessary to pay for taking significant risks. Payments should not be so high as to induce people to take a risk which is perceived as high."[2] Although the guidelines say that payment may be made for risk, it doesn't necessarily mean that they should.

Minimising risk

Risk and hazard should be differentiated. A risk may be low when the hazard is high: a low probability of a serious adverse event. The risk of being struck by lightening is low, but the consequences of this hazard may be fatal.

In the TGN1412 study, risk was considered low. The Duff report establishes that this belief was wrong.[3] Certain drugs by their nature are

the more risky trials—for example, first human testing of new drugs (phase I trials). These are generous decisions for the good of science and society and should be recognised in some way. Money is a pragmatic choice because it can be exchanged for something reflecting the individual's preferences. Paying a supplement recognises the added risk that some volunteers undertake, commending them more highly than others.

Opponents object that higher payment for participation in risky trials is an irresistible inducement. However, in a society where autonomy is highly valued this view is paternalistic. The law fiercely upholds people's fundamental right to choose what to do with their own body, even if that choice may not seem sensible to others.[4] In other areas of life where money is associated with risk, this paternalistic approach is not found. A person is free to make high risk financial investments, even if he stakes his entire savings and property. No one suggests that these decisions are coerced or irresistible. Workers employed in dangerous industries, such as firefighting and mining, are paid a wage premium (colloquially known as danger money), recognising that there is a high risk of serious injury or death. These practices are permitted on the grounds that such services are important to society, that those who do them deserve to be rewarded for contributing in special ways, and that adults should be free to choose the activities they undertake. Subject to the following caveats, payment of volunteers should be viewed in the same way.

"The few studies carried out indicate that money does not affect understanding of risk"

Volunteers' understanding is key

The crux of the issue lies not in esoteric views about money being an undue influence but in volunteers' abilities to appreciate risk. It is well known that money motivates individuals[9]; this in itself is not objectionable. It is also well known that volunteers often fail to appreciate the true risks that a trial poses.[10] However, the most important question is whether individuals' understanding of risk is affected by larger sums of money. Little research has been done on this issue, but the few studies carried out indicate that money does not affect understanding of risk.[11] Indeed, a payment element based on risk would serve as a signalling device alerting individuals to the riskier trials.

To further improve healthy volunteers' understanding of research proposals, specialist independent advisers and recall tests could be introduced for phase I clinical trials. This should be supplemented by better regulation of advertising,[12] some of which has been shown to be misleading and confusing. To ensure that public sector research is not financially out-gunned by private sector money, it would be sensible to adopt some sort of standardised scale for risk payments and to make supplementary risk payments optional or substitutable with appropriate non-monetary benefits.

It has not been shown that an additional risk based payment would reduce individuals' abilities to understand the risks of research and thereby invalidate the consent given. Unless this is shown, it is too paternalistic to prohibit payment according to risk. With the above proposed improvements to research regulation, volunteers' understanding of risks would be improved. The choice to participate could then properly be left to volunteers and their special contribution recognised.

Cite this as: *BMJ* 2009;339:b4142

likely to be of higher risk than others. In particular, the risks are likely to be high if the drugs are biological molecules with novel mechanisms of action, have highly species specific actions, or are directed at immune system targets. First exposure will always carry some risk, even if extremely small. In this case, preclinical development studies did not predict a safe dose for use in humans, even though current regulatory requirements were met. The answer in such situations is not to pay for risk but to proceed more slowly, along the lines outlined in the report: microdosing, low increments in case the dose-response curve is steep, and so on. Predictable higher risk necessitates better precautions: in this way higher (as opposed to high) risk is reduced to a low or minimal level.

"The level of risk should not be so high as to necessitate such payment in the first place"

Agreed payment

Phase I studies in healthy human volunteers could not take place without payment. The basis for levels of payment should therefore be defined. Official guidance is not clear, but risk is not a factor. For example, current guidance from the Office for Protection of Research Subjects states: "In no case should remuneration be viewed as a way of offsetting risks; that is, it should not be considered a benefit to be weighed against study risks. The level of remuneration should not be so high as to cause a prospective subject to accept risks that he or she would not accept in the absence of the remuneration."[4]

The consequences of ignoring such advice have been proved. The deaths of two "healthy" volunteers in phase I studies[5 6] resulted from them withholding information about health factors that would have made them ineligible to participate, thus putting themselves at undue risk. Information was withheld, apparently because they needed or wanted the money offered. Paying healthy volunteers for overt high risk has therefore led to unacceptable risks being taken.

Dickert and Grady described two models of payment that do not take risk into account—wage payment and reimbursement. The wage payment model pays for time, effort, and the endurance of undesirable or uncomfortable procedures. Participation requires little skill, and the level of payment therefore would relate to other unskilled jobs. The drawback is that payment levels would make participation unattractive to better paid people and treating the participant's role as an unskilled job may be seen as inappropriately commercialising participation in research. In the reimbursement model payment is provided to cover expenses, which may or may not include reimbursement for time away from work. This precludes profit, avoids payment for effort or discomfort, and does not depend on the market. It alleviates concerns about undue inducements and gives no incentive to remain uninformed about risks and benefits. Current practice in the UK is a fudge: the guidance available from INVOLVE, the organisation aimed at encouraging participation in medical and social research is a mixture of both models.[7]

There will always be a tension between the need to recruit research participants and the obligation to protect them. Economic principles predict that for otherwise undecided individuals, incentives act as inducements. Financial benefits are the most tangible incentive, even if their effect will vary among different groups of people. Volunteers in phase I studies should therefore not be paid for risk.

Cite this as: *BMJ* 2009;339:b4145