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.

**YES** The severe reactions experienced by healthy volunteers in the TGN1412 (Northwick Park) trial have led to questions about payment for participation. 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 for the higher risks in some trials and, secondly, because it is inconsistent with other practices in society.

**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.” 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.” 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 lightning 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. Certain drugs by their nature are certainly more dangerous than others, and yet they may not be considered high risk under the current guidelines.

All references are in the version on bmj.com
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 indi-
vidual’s preferences. Paying a supplement rec-
ognises 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 irresponsible inducement. However, in a society where auton-
omy 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.7 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 irresponsible. Workers employed in
dangerous industries, such as firefighting and mining, are paid a wage premium (colloqui-
ally 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.

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 individuals8; 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
conducted 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.

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likely to be of higher risk than others. In particu-
lar, 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 develop-
ment 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.

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 guid-
ance from the Office for Protection of Research
Subjects states: “In no case should remunera-
tion 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 remu-
neration 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.”

The consequences of ignoring such advice have been proved.
The deaths of two “healthy” volunteers in phase I studies13 resulted from them withholding information about health fac-
tors that would have made them ineligible to participate, thus putting them-
selves at undue risk. Information was withheld,
apparently because they needed or wanted the
money offered. Paying healthy volunteers for
over high risk has therefore led to unaccept-
able risks being taken.

Dickert and Grady described two models of
payment that do not take risk into account—
only 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 par-
ticipation 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 par-
ticipation 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 individu-
als, 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.

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