Risk, Helsinki 2000 and the use of placebo in medical research

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ABSTRACT – There has been vigorous debate over the use of placebo controls in clinical trials in human subjects where active treatments are already in widespread use. The debate has extended from the use of placebo controls in trials of products for AIDS in developing countries to the use of placebos in trials in conditions such as mild hypertension, asthma, depression, chronic stable angina etc. Some have argued that placebos can never be justified where an active treatment exists. By contrast, we believe that minor levels of risk are justified in healthcare research under defined conditions provided there is full information and consent. The opportunities for altruism in research should neither be exploited nor prevented.

KEY WORDS: Declaration of Helsinki, equivalence trials, placebo, research ethics

Risk outside the context of healthcare

'One small step for a man, one giant leap forward for mankind'. The words were of course those of Neil Armstrong, the first man on the moon. For Armstrong, his achievement was not merely personal, but something more: it was something for mankind. Armstrong's arrival on the moon demonstrated that man could travel there – and return. To do this required skill, dedication and courage; it also involved high risk. The Challenger disaster taught us graphically that those who participate in this adventure of discovery risk their lives.

Should this be permitted? Generally we ignore calls to ban mountaineering, or single-handed ocean racing or whatever has led to the latest disaster or heroic rescue because we think that autonomy allows people to choose courses of action that others may think irrational. As Mill suggested, we usually get seriously exercised about dangerous behaviour only when that behaviour poses a risk to others. Let us accept that the moon shot was a legitimate scientific experiment, to demonstrate new possibilities, to bring back samples for further analysis, to make new measurements. Let us accept that the new knowledge is or may be important. Should volunteers have been *invited* to take so great a risk? Was the knowledge (or the prestige) sufficient to justify the risk to Armstrong's life? Most people would probably think it was sufficient. Astronauts, after all, know the risks. It does not seem too difficult for NASA to recruit volunteers.

Other activities in which new knowledge is being sought also involve risk. New planes need test pilots to fly them, new cosmetics human subjects to try them. Dyestuffs, food additives, every conceivable type of equipment must be assessed for efficacy and safety before being brought to market. In every case, someone must take the risk and use the product for the first time. Safety and efficacy must be assessed before it is sold to the public. Usually the risk is low, of course, but it is a common feature of commercial life. There is nothing conceptually different about clinical trials. Society could not develop (avoiding the more contentious term 'progress') without trials of new products.

Healthcare research: the healthy volunteer

In human healthcare research, participants come in two groups: healthy volunteers and patients. The difference between the two is that the patient has a relationship with a professional, and to that degree is vulnerable both to the accuracy and appropriateness of the advice and to the authority and power relationship that stems from the inequality in knowledge.

Healthy volunteers are often paid to participate in the assessment of new techniques, including phase I trials of new drugs. Such research is well regulated and serious adverse outcomes are rare. Ethics committees advise whether the risks are acceptable. Given that the subject is healthy, there is of course no benefit – except the payment to participate. That payment is generally agreed to be ethical provided that it does not induce the subject to undertake unreasonable risks. Defining 'unreasonable' or 'inducement' involves drawing a line through a grey area – as of course do many important judgements made by society or individuals every day, for example:

- what counts as old age (and a pension)
- wealth (and higher taxation), or
- disability (and entitlements).

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Key Points

- **Many human activities involve risk, both in the workplace and in the search for new knowledge**
- **Medical research is an example of this, both in healthy volunteers and in patients**
- **Some risk is generally agreed to be permissible in nontherapeutic patient studies even where these involve administration of pharmaceuticals**
- **Risk may be involved in clinical trials in which a placebo is used when a proven or widely accepted treatment is already available**
- **Some have argued that such studies are always unethical, but there may be clear methodological benefits**
- **Provided that patients receive clear and explicit information on which to base their consent, it is ethical to conduct such studies under prescribed conditions**

There can be no unanimity of judgement. Reasonable people will reach differing conclusions, even starting with identical moral principles. The best to hope for is some sort of consensus.

Some healthy volunteers may participate in physiological research, in studies aimed at elucidating the mechanisms or responses to particular stimuli. Such studies may even involve administering pharmaceuticals or invasive monitoring, such as:

- pressure transducers in the bladder
- arterial or venous catheters
- biopsies, and
- blood sampling.

Many of these studies are conducted in academic departments and, as with phase I drug studies, are assessed independently for risk.

If physiological understanding is a prerequisite for other benefits, such as the understanding of disease and the increase in human life or happiness, then properly regulated research of this sort should be encouraged. It is morally good, as is the development of new drugs. The same could be said about new planes, cosmetics, additives, dyestuffs, equipment – although controversially in some cases.

Research in patients: the difference

For patients, however, the investigator faces a difficulty which stems from the therapeutic relationship:

> *In providing medical care for patients, the physician makes observations, investigates, tests hypotheses and experiments with different treatments. Moreover, the exemplary physician is always learning how to improve treatment for future patients on the basis of clinical experience with current patients and familiarity with the medical literature.*[1]

When doctors go beyond the practice of what has been established for other similar patients or what is believed to be best for a given patient and instead aim for new knowledge in a novel protocol, medical care is confused with clinical research. Patients expecting their physicians to treat their illnesses, and trusting them to act in their best interests, may find they are invited to contribute to new scientific knowledge. Such a protocol may be entirely nontherapeutic; a new technique may need to be validated or the mechanism of disease be elucidated in a study that may be either noninvasive or invasive, using cannulae, other procedures, isotopes, infusions and so on.

All qualitative research in patients, for example, is nontherapeutic and noninvasive in this sense, as are questionnaire studies or simple measurements such as height and weight. The important regulatory features are again those for all human research: the principles of minimal risk and of consent. The primary principle is, of course, minimal risk. In subjects unable to give consent, it is the only protection available, while for those able to consent, research would be unethical if the risks were high regardless of consent. Notwithstanding the motivation and understanding of the subject, physicians would not permit any study with the risk of a moon shot. Armstrong's participation in research would not get through the ethics committee.

Why do patients participate in research?

There are several reasons why patients may participate in research where there is no possibility of therapeutic benefit:

- some may wish to please the professionals
- other patients may feel an obligation to help after kindly care
- they may have a genuine interest in science in this information age, and
- because of a genuine altruism to take a small risk or to give a small amount of time, in order to further knowledge.

In general, the investigator is not very concerned with the reasons behind the decision to participate. Provided the risks are small, the patient understands what will be done and has given consent given, the investigator can proceed.

The possibility of altruism should be neither abused nor discouraged. In the nonresearch context, thousands accept the minimal risks of venepuncture and syncope to give blood; the health services could not function as well without such altruism. The fact of being a patient and therefore, in our terms, vulnerable is a reason for effective regulation against abuse or exploitation and for ensuring that risk is minimal and fully understood. It is not a reason for abandoning all research where true equipoise cannot exist. There can be no equipoise in nontherapeutic research.

The risks of treatment

Even in clinical care, and even under supervision, risks are sometimes greater than the 'best proven prophylactic, diagnostic and therapeutic methods'. Someone has to be the first patient to be the subject of a procedure. Despite dual controls, learner drivers do drive into lamp posts. These risks can be justified because there is no alternative.

There is a risk in being offered treatment in ordinary practice, whether or not there is proof of benefit, as all treatments are potentially harmful. Doctors sometimes offer patients treatment (or investigations) without proof of benefit. Many treatments are neither validated in clinical trials nor are their net benefits so obvious in clinical practice that a trial is unnecessary. The reasons for this may be historical, in that the agent was introduced before the era of drug licensing and randomised trials. In other cases, the trials do not provide adequate evidence, so the benefits of treatment must be extrapolated from existing knowledge. In clinical practice, the doctor is often not in equipoise and will recommend unproven treatment as being in the patient's best interest. By contrast, there is risk in being offered no treatment if a treatment exists that is not being used. Sometimes that treatment is of traditional use, frequently used by other doctors and sometimes of proven value.

When is use of a placebo justified?

When might no treatment be offered in the investigational setting, and when can a placebo be justified? The high profile debate has been about the use of placebo, but the basic ethical question concerns the acceptability of withholding treatment. Before contemplating using a placebo, physicians must be satisfied that it is acceptable to leave certain patients untreated. Although placebo is not the same as no treatment, and doubt has been cast on the extent of the placebo effect, clearly a placebo comparison with insulin in type 1 diabetes is not appropriate. We can agree that a new therapy can be compared against no therapy when no therapy currently exists, provided there is genuine uncertainty about the risk/benefit balance of the new agent. This is termed equipoise. Bias is removed in the trial by the use of placebo in the non-treatment group. In some instances, of course, the pretrial data may make it unethical to do a randomised trial and the issue of placebo does not arise, given the historical controls. (It might be speculated that this is part of the perception in the recent past with anti-HIV agents.) In other situations, ethics committees are often faced with assertions about 'no proven therapy' when therapies exist and are in quite widespread use, but have never been licensed for the indication under the test proposed.

Far greater controversy has arisen over the use of placebo where treatments are agreed to exist, but their omission creates risks thought to be acceptably low or minimal. The reasons for the heated nature of this controversy are four-fold, only the first of which will be discussed here:

1. The Declaration of Helsinki appears to prohibit such studies *regardless* of the level of risk.
2. Placebos have been used in unjustifiable circumstances when the discomfort or risk to patients cannot be justified and, partly as a consequence, there is widespread suspicion of drug companies.
3. The demands of the Food and Drug Administration (FDA) are seen as slanted towards the interests of the industry.
4. The controversy has been associated with the debates on placebo-controlled trials on drugs likely to be used almost exclusively in the First World, but in which the trial is taking place in the Third World where, so the argument runs, placebo can be justified because that is all that would otherwise be available to those randomised to it.

The Declaration of Helsinki and its revisions

Since 1964, the Helsinki Declaration has been through five revisions, the most recent at Edinburgh in October 2000. In 1999, the controversy arising from the trial of zidovudine[2] led to proposals from the American Medical Association to amend the Declaration with respect to the use of placebos. One proposal stated that:

> *when the outcome measures are neither death nor disability, placebo or other no-treatment controls may be justified on the basis of their efficiency.*

As commented by Brennan,[3] the use of efficiency as a value exemplifies the tug of the marketplace. In the American context, it was noted that the experience of managed care does not demonstrate that the marketplace is able to tolerate well the principle of commitment to an individual patient or research subject. This proposal was not accepted, and the controversial Article 29 now reads:

> *The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.*

This has not stopped the debate of course. Long-standing regulations in the European Union state only that in some instances it may not be appropriate to use a placebo as a comparator, and hence, by implication, that in many instances a placebo would be appropriate.[4] More recently, the European Agency for the Evaluation of Medicinal Products supported the judicious use of placebo, even in the context of proven treatment, when such use is essential and does not pose a risk of irreversible harm.[5] In the USA, the FDA expresses a strong preference for placebo studies in situations where risks are low, even if not minimal.[6] The result has been that in 2002 the World Medical Association (WMA) issued a note of clarification on Article 29 – a hitherto unprecedented step:

> *The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:*
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> - *Where for compelling and scientifically sound methodological reason its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or*
> - *Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.*

This clarification effectively authorises the use of placebo on at least a limited basis and, moreover, a basis unacceptable to some. Thus, using the second criterion, it might be acceptable to use placebo in a trial of a new drug, for example, for eczema and let the placebo-treated patient scratch.[7]

Justifying placebo controls where therapy exists

Against this, it has been pointed out that proven care is withheld from patients in the experimental arm of a trial in which the control is the new active treatment. This is in line with the Declaration because patients in the experimental group receive at least *some* form of treatment, so treatment *per se* is not withheld. Those who support the use of placebo point out, first, that patients in a placebo group may receive adjunctive treatment and, secondly, that patients in the placebo group in some placebo-controlled trials have fared better than those eligible for the trial but who declined to participate and instead received standard care. Hence it is understandable that standards based on the level of risk and careful monitoring of subjects seem reasonable.[8]

A trial cannot be justified if it is likely to fail to deliver an answer. If a placebo is essential for scientific reasons, that is an ethical reason for its use – a necessary, but not a sufficient one. Placebo controls may be considered, for example, where substantial numbers of patients receiving placebo have measurable and clinically meaningful improvements; this is a common observation in patients with headache, arthritis, minor psychiatric illness, hypertension and so on. If an inactive placebo is not used in such trials, the treatment (and placebo) effects of the new drug may easily be obscured by the effects of the clinical attention received by both groups. Therapies of known efficacy may be no better than placebo in some trials because of variable responses in particular populations, unpredictable and small effects, and high rates of spontaneous improvement. Without a placebo group, finding no difference between the new and standard treatments can be misleading or uninterpretable.[9] The more important issue arises in equivalence trials.[9–11]

In equivalence trials, larger samples are required to achieve sufficient power because the difference between the rates of response to the two drugs is likely to be smaller than that between the rates of response to an investigational treatment and placebo. The result, depending on the likely difference, is that the trial must recruit a substantially larger number of subjects using a standard therapy as comparator. As a result, if the rate of response is lower than the standard drug, albeit still within the 10% range for equivalence, more participants will be harmed by not receiving the standard treatment than if a placebo-controlled trial were conducted.

It may be concluded that it is simplistic to argue that placebo-controlled trials necessarily sacrifice the well-being of patients. It may be true that it is cheaper to run a trial to show superiority against placebo as it can be shown with fewer patients. It is also accepted that pharmaceutical companies want to show that their new product is effective, not that it is as, or even slightly less, effective than a comparator – but such a trial design may also protect more subjects. If subject protection is the first duty of any ethics committee, such a design is to be preferred in these circumstances.

The following recent blanket statement is an oversimplification, and not one that we can support:[12]

> *the use of a placebo can never be justified when a drug of proved efficacy is already available for a given therapeutic indication*

We would instead agree with Collier's 1995 view that there is a need to revise the blanket Helsinki recommendations which undermine the use of placebos generally.[13] So-called 'me too' drugs sometimes turn out to have significant advantages over older preparations; these are not always initially apparent. Equivalence trials will continue to be necessary as long as such compounds are developed, and placebo controls will continue to be needed for sound methodological reasons.[14] These compounds are necessary for a healthy pharmaceutical industry to maintain profitability while continuing to develop genuinely novel drugs. Nor is profitability itself necessarily morally suspect in a capitalist world marketplace. Paternalistically depriving the patient of the choice of taking part in such placebo-controlled studies removes an opportunity for altruism. The important aspect to emphasise is the clarity of the information upon which consent is based. This is an essential responsibility of everyone involved in ethical research, but especially of the ethics committee and the individual investigator talking to the patient. No one should propose participation in a study with the risks of a Neil Armstrong, but a much more modest risk may be justified in ordinary non-medical life, in human volunteer research and in non-invasive research in patients. We see no reason why these considerations should not apply in therapeutic research, even when proven therapy is available, albeit in strictly limited circumstances.

Guidance other than the Helsinki Declaration

In general, the Royal College of Physicians of London 1996 guidelines[15] followed the guidance of the Council of International Organisations of Medical Sciences (CIOMS). The latest CIOMS *International ethical guidelines for biomedical research*[16] provide a clear summary of good practice:

> *As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention. In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo or 'no treatment'. Placebo may be used:*
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> - *When there is no established effective intervention;*
> - *When withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms;*
> - *When use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects.*

Definitions of risks of minimal harm have been made as those that are similar to risks taken in every day life. These vary enormously: people who ski or hang-glide take far greater risks than those who rarely leave their houses, and far more than those who participate in most placebo-controlled studies. However, the risks to which people are allowed to subject others should be regulated, as opposed to those risks that people choose to take for themselves. The Council of Europe suggests that:

> *the research bears minimal risk if it is to be expected that it would result, at the most, in a very slight and temporary negative impact on the health of the person concerned.*[17]

The responsibility to determine acceptable risk falls to those who design trials and those who regulate them. Above all, the patient must decide on the basis of clear and explicit information. If patients are vulnerable by virtue of their status, the answer is not to remove their discretion but to inform it. We believe that at least some anxieties would be helped if patient organisations or consumer groups were to be involved in trial design.[18,19] Armstrong had well informed discretion and a high risk. Patients should be protected, but their altruism should be encouraged, provided that risks are low and justifiable. Debates surrounding the revisions of the Declaration of Helsinki are best seen in a broader context of risk where individuals may volunteer to take small risks for a greater good.

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