Department of ethics

Placebo-controlled trials and the Declaration of Helsinki

John A Lewis, Bertil Jonsson, Gottfried Kreutz, Cristina Sampaio, Barbara van Zwieten-Boot

A revised version of the Declaration of Helsinki, issued in October, 2000, remains a vital expression of medical ethics, and deserves unanimous support. A strict interpretation of the declaration seems to rule out clinical trials that use a placebo control group whenever licensed therapeutic methods already exist, preferring active controls. Although the efficacy of some new medicines can be satisfactorily established without the use of a placebo, for others the judicious use of placebo remains essential to establish their effectiveness.

There are several circumstances in which placebo-controlled trials offer the only feasible way forward and are widely accepted as ethical despite the availability of approved alternatives. Provided that the conditions that ensure the ethical nature of these trials are clearly understood and implemented, the Committee for Proprietary Medicinal Products (CPMP) take the view that their continued use for this purpose is necessary to satisfy public-health needs.

Revised Declaration of Helsinki

The Declaration of Helsinki, first drawn up in 1964, has become standard guidance for all medical research that involves human beings. In particular, it has been widely used to guide the conduct of clinical trials done to develop new medicinal products. The revision of the declaration,[1] issued by the World Medical Association in October, 2000, has been appropriately strengthened in several areas and its relevance and value remains as great as ever. However, the new version contains one section, section 29, which could cause substantial difficulties for the future development of medical products if it is interpreted literally and implemented universally. Section 29 (panel) is in the part of the declaration that deals with principles for medical research combined with medical care.

The purpose of section 29, like many other sections, is the highly laudable one of ensuring that patients are not disadvantaged or exploited when they take part in clinical trials. A specific concern often voiced is that individuals from less-developed countries might be used in research for the benefits of those in more-developed countries.[2–5] For example, a placebo-controlled trial of an anti-HIV product might be cheaper and more feasible to do in a less-developed country, where few such drugs are widely used, than in, say, the European Union. In this article, we do not seek to suggest that such practices are acceptable, and we acknowledge that these and other ethical abuses of placebo can arise in any country and should be eliminated.

The difficulty is, however, that the wording of section 29 also seems to rule out some vital uses of placebo-controlled trials in areas of medicine in which proven prophylactic, diagnostic, or therapeutic methods already exist. The section makes no exception for trials done in the specific population of patients who would subsequently benefit from a successful outcome of the research, even when there is adequate patient consent and careful avoidance of any irreversible harm or other ethically unacceptable consequences, such as long-term severe pain.

Wording of section 29

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, where no proven prophylactic, diagnostic or therapeutic method exists.

There was a section similar to section 29 in the previous version of the declaration, and it is the absence of clarification that has generated our concern. In reference to the previous version, Rothman and Michels[6] noted the inconsistency between principle and practice, asserting: "studies that breach this provision of the Declaration of Helsinki are still commonly conducted, with the full knowledge of regulatory agencies and institutional review boards". They went on to question the excessive and unethical use of placebo, particularly in the development of new medicinal products. We do not claim, therefore, that this debate is a new one, but that the uncertainties generated by the revised version of the declaration make it important that the position taken by the CPMP[7] is explained.

Our three aims are, therefore, to explain why trials against placebo are sometimes scientifically necessary to obtain sufficient proof of the efficacy of a new medicinal product, irrespective of the treatments that are already available; to outline some design strategies that avoid the apparent ethical dilemma; and to describe how and when placebo-controlled trials can be ethically done, in our opinion, if no alternatives are available.

Throughout the article the emphasis is on the assessment of the efficacy of a therapeutic medicinal product, but the same considerations apply to prophylactic and diagnostic agents and methods. The need to avoid any harm to the patient is kept clearly in mind. The focus of attention is the nature of the control group; the importance of assessment through randomised controlled trials is assumed. Although we concentrate on the particular circumstances when placebo control is important, this angle should not be taken to imply that active controls are uninformative. There are many situations when a three-group study, with placebo and active controls, is the design of choice.

Lancet 2002; **359:** 1337–40

Hatch Green Cottage, Chartham Hatch, Canterbury, Kent CT4 7LP, UK (Prof J A Lewis DSc)**; Medical Products Agency, Uppsala, Sweden** (B Jonsson MD)**; Bundesinstitut fur Arzneimittel und Medizinproducte, Bonn, Germany** (G Kreutz MD)**; Lisbon School of Medicine, Hospital de Santa Maria, Lisboa, Portugal** (Prof C Sampaio MD)**; Medicines Evaluation Board, Den Haag, Netherlands** (B van Zwieten-Boot PhD)

Correspondence to: Prof John A Lewis (e-mail: johnlewis@clinitrial.co.uk)

Clinical trials of new medicinal products

A wide variety of clinical trials are done during the development of a new product, in healthy individuals and in patients. The trials that could be affected by section 29 are done in phase III, and sometimes the later part of phase II. They are the trials done in patients with the target disease to provide pivotal evidence of efficacy. In such trials, the product should generally be tested in the planned manner of use in the intended population. Hence medical research is combined with medical care, and section 29 would seem to apply.

Regulatory authorities have a duty to ensure that the evidence of efficacy is convincing, and that the degree of efficacy is sufficiently substantial to outweigh any safety risks or problems with side-effects. Authorities rely heavily on robust evidence from reliable phase III controlled trials. Any inadequacies of these data can lead to mistakes. For instance, marketing authorisation might be mistakenly granted or mistakenly withheld. Alternatively there could be delays in granting authorisations, with consequent delays in the availability of the corresponding medical benefits. All of these outcomes are undesirable, especially if based on clinical trials with foreseeable and avoidable ambiguities. Such trials can surely be held to be unethical from every perspective, including that of the patient.

We contend that the use of active-controlled trials instead of placebo-controlled trials would, in some circumstances, reduce the reliability of clinical trial conclusions and hence increase the proportion of wrong decisions. However, we recognise that there are other circumstances in which active controls might be sufficient to reach reliable conclusions with respect to efficacy, and that active controls can provide valuable supportive evidence in development of many drugs.

Advantages of placebo-controlled trials

There are well known reasons why placebo-controlled trials are generally more reliable than active-controlled trials in provision of conclusive proof of efficacy. The reasons are fully discussed in the E10 guideline *Choice of Control Group*,[8] which was produced under the auspices of the International Conference on Harmonisation (ICH) and has been adopted in Europe, USA, and Japan. Other guidelines and publications also refer to this issue.[9–11]

Briefly, placebo-controlled trials provide their own check of internal validity. A positive difference in efficacy, when detected in a well designed and implemented placebo-controlled trial, means, first, that the trial is capable of detecting differences, and, second, that the test treatment is more efficacious than placebo. Furthermore, for regulatory purposes, a satisfactory analysis of a placebo-controlled trial will be judged conservative—ie, to indicate the minimum effect plausibly due to the test treatment. This judgement ensures that treatments with statistically significant but clinically inadequate effects are identified, and results in appropriately cautious licensing decisions.

Improvement over an active control

Some active-controlled trials have similar methodological strengths, namely those aiming to show the improved efficacy of the test product. Showing that a test product has improved efficacy compared with an already licensed product is clearly a satisfactory result, and has the same reassurance with respect to the internal validity of the trial. However, it is noteworthy that in comparative clinical trials many potentially valuable new medicinal products do not have greater efficacy than previously licensed products. Their advantages might lie in other areas, such as improved safety, tolerability, convenience of administration, or compliance. Furthermore, the drugs might provide necessary alternatives to cover individual instances of intolerance to treatment or resistance to beneficial effects. Important benefits of this nature might only become apparent as time progresses. Hence, any requirement that new medicinal products should show improved efficacy would rule out these important advances and would be deleterious to public health. Section 6 of the declaration, which states that the primary purpose of medical research is the improvement of treatment, should surely be interpreted in this light—improvement should indeed be sought but not necessarily in average efficacy.

Similar efficacy to an active control

The methodological difficulty that results in the continuing need for placebo-controlled trials relates to active-controlled trials intended to show that two treatments have similar effects. Similarity is a far more likely objective in practical situations, in which active controls might be considered. Such trials are often set up as non-inferiority trials rather than equivalence trials. In these studies, similarity or superiority to the active control are both regarded as satisfactory outcomes, and only inferiority as unsatisfactory. However, similarity is the most reasonable expectation.

Demonstrations of non-inferiority without the use of concurrent placebo have to rely solely on indirect evidence that a trial is capable of showing clinically important differences (if they exist), that is, that the trial has sufficient sensitivity. However, a trial that lacks sensitivity is difficult to distinguish from one that does not. When trial sensitivity is uncertain, specification of the degree of difference that should be regarded as clinically important is difficult. Absence of trial sensitivity can derive from two possible sources. The first is the inconsistency of trial results. In some areas of medicine definition of circumstances under which treatment effects can be reliably replicated has proved impossible. For example, in the treatment of depression, placebo-controlled trials have produced variable results for established antidepressant drugs, sometimes identifying treatment effects and sometimes not.[12] Despite the undeniable clinical value of antidepressives, these circumstances have frequently led to the need for several placebo-controlled trials to provide convincing evidence of efficacy. When a non-inferiority trial is done in such an area, there is no way of knowing whether an apparent absence of difference between treatments is really due to the failure of the trial.

The second source of lack of sensitivity is the quality of the trial, largely in relation to the way it is done. Nearly all of the many possible difficulties and inadequacies in trial conduct have a similar effect—they tend to pull the treatment groups together and favour an incorrect conclusion of no difference. Hence for an active-controlled trial to be reliable it must be done in an area of medicine in which the circumstances that lead to medicines showing their effects, and showing consistent sizes of effects, can be defined—there must be historical evidence to back that definition up. In addition, the trial must be done to standards that have previously been seen to detect consistent differences from placebo—eg, a similar protocol (similar population of patients, same endpoints, trial procedures, &c) should be applied by staff with closely related experience. The trial should also be scrutinised for departures from the protocol and other failures. There should be evidence in the trial that the treatments had the expected degree of activity, for example by comparison of

the results on the active comparator with those from earlier trials, or by examination of changes from baseline, if relevant. This collection of conditions is hard to meet in practice. Although checks can be effected as described, complete avoidance of a degree of assumption is impossible.

An additional complication is that the results of a non-inferiority trial nearly always leave open the possibility that the new treatment really does display a degree of inferiority to the standard treatment. This difficulty is an inevitable consequence of statistical variation, even when the new and standard treatments are truly equivalent. The extent of the potential inferiority depends on the true relative efficacy of the two treatments and the precision of the trial. However, when the benefits of the active comparator are small or when the outcome is death, any erosion of benefit might be difficult to envisage when licensing a new treatment for the same disease. The average beneficial effect of treatment is relatively small in urinary incontinence compared with other diseases, for example, as is also the case with Alzheimer's disease. Furthermore, experience of clinical trials in Alzheimer's disease is in its infancy. Hence, in this instance there is neither a firm basis for specification of the size of a clinically important difference nor sufficient experience of clinical trials to be confident that an observed effect size could be replicated.

Because of the difficulties associated with active-controlled trials, even in well-researched and reliable areas, common practice is to be cautious and to prespecify as clinically important a smaller difference than simple calculations might suggest. This move is not only intended to minimise the potential loss of efficacy but also to compensate for any unintended deficiencies in the quality of the trial.

Finally, the evolution of medical practice might make it impossible to find placebo-controlled trials of the active comparator to use as a reliable basis for judging the importance of a difference.[13] Standards of care improve with time, changing the nature of the patient population and adding new medicines and new surgical procedures. For example, the benefits of beta blockers after myocardial infarction were established before the routine use of angeotensin-converting enzyme (ACE) inhibitors and thrombolytic agents, and many other changes to medical and surgical practice. We can no longer assume, therefore, that the size of mortality reduction shown by overviews in the 1980s[14] still applies. However, a reassessment of beta blockade after myocardial infarction by means of new placebo-controlled trials would be impossible, and hence the use of a beta blocker as an active comparator in this indication would not be satisfactory.

Rothman and Michels[6] do not seem to have appreciated these serious methodological deficiencies of active-controlled trials. Despite these deficiencies, in some areas of medicine reliable and conclusive active-controlled trials can be done and might be sufficient for licensing purposes.

Designs that reduce exposure to placebo

Even in a straightforward placebo-controlled trial, receiving placebo does not imply receiving no medical treatment. In most trials there will be other medications that are permitted in both treatment groups and that are expected to be used to a roughly similar extent. Rescue medication will be predefined, when appropriate, for use in circumstances described in the protocol. Additionally, a standard condition in all clinical trials is that at any stage patients can withdraw, either from randomised treatment or from the trial. In studies designed to show improvement of symptoms, time to withdrawal might also be used as a relevant measure of efficacy, thereby reducing the incentive to prolong treatment with placebo.

There are other manoeuvres that are available. Patients could be randomly assigned to test treatment or placebo as well as standard medication. Thus in trials in chronic heart failure, all individuals might receive ACE inhibitors and diuretics, and a new agent has to show its effect on top of those treatments. If this work were successful, then future trials might explore whether the new treatment allowed ACE inhibitors or diuretics to be tapered off.

In some placebo-controlled trials every patient is kept on their randomised medication until they deteriorate to a predetermined, and acceptable, extent. The time to this deterioration can then be the primary endpoint of the trial. In multiple sclerosis, for example, the time to the next exacerbation might be chosen. Similar considerations apply to trials in which the time to taking rescue therapy is recorded. This method might be appropriate in some types of pain study.

Finally, it is sometimes more acceptable to assess whether a test treatment can be withdrawn after time. Thus, after 3 months on a test treatment for depression, patients might be randomised to continue on test or to receive placebo. Detection of a difference is a reliable piece of evidence of longer-term efficacy.

Ethically acceptable use of placebo control

Although alternative designs are always available, they often do not provide satisfactory answers. Straightforward randomised placebo-controlled comparisons are generally scientifically desirable for reliable evidence of efficacy, even when active treatments are already in widespread use. In what circumstances can such trials be ethically done?

In this connection it is important to draw a distinction between signs and symptoms that the patient could have without any irreversible harm, those that indicate the possibility of irreversible harm, and indeed the irreversible harm itself. Mild-to-moderate migraine would fall into the first category and severe hypertension would fall into the second. Events such as myocardial infarction and stroke clearly constitute irreversible harm.

When efficacious treatments are available, many triallists believe that to administer placebo for a certain period is still ethically acceptable in certain circumstances—ie, circumstances when the period on placebo, and therefore not on the known effective agents, does not entail any additional risk of irreversible harm to the patient; when the patient, or their legal representative, is capable of providing, and provides, fully informed consent; and when the patient can request conventional treatment at any stage, or can be placed on such treatment by the treating doctor. These conditions are in line with the remainder of the Declaration of Helsinki—other than section 29—and are emphasised in the ICH E6 guideline on *Good Clinical Practice*.[15]

Several aspects of this statement need further clarification. Placebo-controlled trials, designed to show a reduction in irreversible harm, are unacceptable if therapies that already have this effect are available and acceptable to the patients of interest. Long-term placebo-controlled trials in patients with hypertension are, therefore, considered unacceptable, whereas short-term trials might be satisfactory. Furthermore, the trial procedures should involve careful and regular monitoring of the patient throughout the placebo (or test treatment)

period to detect any early signs of serious trouble. Such surveillance could in fact result in the patient receiving a better standard of care than would have been the case outside the trial, so that their risks might actually be reduced relative to standard treatment. In ascertaining whether fully informed consent has been provided, the patient (or their legal representative) must be capable of understanding the nature of the clinical trial in which they are due to participate, and the symptoms and risks that they would be expected to endure. They should also be told the nature and benefits of the standard treatments that they would be denied and should understand their right to withdraw at any stage. However, seeking of informed consent can never provide an adequate defence of an inherently unethical trial.

Rothman and Michels[6] do not believe that the seeking of informed consent alleviates the difficulties with any placebo-controlled trials. In particular, they emphasise the fact that the patient is unlikely to be aware of the possibility of use of an active control. In areas where active-controlled trials are unreliable, this point does not seem tenable. Patients will surely only wish to take part in research that can produce reliable and informative conclusions. Trials that cannot do so must be regarded as unethical.

We do not claim any special expertise in the field of ethics. However, we suggest that the rights of individuals should be protected when doing clinical trials, and also that the treatment of the individual patient should be evidence based. As we have indicated, there are areas of medicine where reliable evidence of efficacy can only be generated by placebo-controlled trials. In this respect, limitations on the use of this design will work to the disadvantage of the patient and should be avoided whenever possible. For this reason, we propose that a revised wording of section 29 should be sought.

Conclusion

Although our view of the ethicality of placebo might seem inconsistent with the meaning of section 29 of the declaration, it echos widely held opinions.[16,17] There are several areas of medicine in which licensed products are available, but in which placebo-controlled trials still remain the only means of conclusively assessing the efficacy of new medicinal products whose potential advantages lie in areas other than efficacy. Provided that the safety and interests of individual patients are carefully protected, the conduct of placebo-controlled trials in these situations remains vital if correct regulatory decisions are to be made on the basis of reliable research.[7] This outcome is clearly in the best interests of patients.

Prof J A Lewis was a CPMP Expert until July, 2001; B Jonsson is Vice Chair and G Kreutz is a member of CPMP Efficacy Working Party; Prof C Sampaio is a CPMP Member; and B van Zwieten-Boot is a CPMP Member and Chair of CPMP Efficacy Working Party.

References

1 World Medical Association. Declaration of Helsinki (as revised). www.wma.net/e/policy/17-c_e.html (accessed Jan 17, 2002).
2 Christie B. Doctors revise Declaration of Helsinki. *BMJ* 2000; **321:** 913.
3 Shapiro HT, Meslin EM. Ethical issues in the design and conduct of clinical trials in developing countries. *N Engl J Med* 2001; **345:** 139–41.
4 Koski G, Nightingale SL. Research involving human subjects in developing countries. *N Engl J Med* 2001; **345:** 136–38.
5 Moreno JD. Placebos on trial. *Ann Neurol* 2001; **49:** 558–60.
6 Rothman KJ, Michels KB. The continued unethical use of placebo controls. *N Engl J Med* 1994; **331:** 394–98.
7 Committee for Proprietary Medicinal Products. EMEA/CPMP Position statement on the use of placebo in clinical trials with regard to the revised Declaration of Helsinki. www.emea.eu.int/index/indexh1.htm (accessed Jan 17, 2002).
8 Anon. Choice of control group in clinical trials, ICH topic E10. London: EMEA, 2000.
9 Anon. Statistical principles for clinical trials, ICH topic E9. London: EMEA, 1998.
10 Committee for Proprietary Medicinal Products (CPMP). Points to consider on switching between superiority and non-inferiority. London: EMEA, 2000.
11 Jones B, Jarvis P, Lewis JA, Ebbutt AF. Trials to assess equivalence: the importance of rigorous methods. *BMJ* 1996; **313:** 36–39.
12 Storosum JG, Elferinck AJA, van Zwieten BJ, van den Brink W, Gersons BPR, Broekmans AW. Short-term efficacy of tricyclic anti-depressants revisited: a meta-analytic study. *Eur J Neuropsychopharmacol* 2001; **11:** 173–80.
13 Siegel JP. Equivalence and non-inferiority trials. *Am Heart J* 2000; **139:** 5166–70.
14 Yusuf S, Peto R, Lewis JA, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomised trials. *Prog Cardiovasc Dis* 1985; **27:** 335–71.
15 Anon. Good clinical practice, ICH topic E6. London: EMEA, 1997.
16 Temple R, Ellenberg SS. Placebo-controlled trials and active-controlled trials in the evaluation of new treatments, part 1: ethical and scientific issues. *Ann Intern Med* 2000; **133:** 455–62.
17 Temple R, Ellenberg SS. Placebo-controlled trials and active-controlled trials in the evaluation of new treatments, part 2: practical issues and specific cases. *Ann Intern Med* 2000; **133:** 464–70.