For and against

Declaration of Helsinki should be strengthened

Kenneth J Rothman, Karin B Michels, Michael Baum

The World Medical Association is now debating the next revision of the Declaration of Helsinki. Kenneth Rothman and Karin Michels argue that critics of the declaration, notably the US Food and Drug Administration, are trying to give scientists greater latitude than the declaration allows. In particular, Rothman and Michels dispute the morality of performing placebo controlled trials when there is an existing accepted treatment, and they offer other suggestions to strengthen the protection of patients who participate in medical experiments. Michael Baum argues against their absolutism on this issue and against what he considers their anti-science stance

Department of Epidemiology and Biostatistics, Boston University School of Public Health, Boston University Medical Center, Boston, MA 02118-2526, USA
Kenneth J Rothman
professor

Harvard Medical School Obstetrics and Gynecology Epidemiology Center, Brigham and Women's Hospital, Boston, MA 02115, USA
Karin B Michels
assistant professor

Correspondence to
K J Rothman
KRothman@bu.edu

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FOR Actions that penalise some for the good of others are defended under the utilitarian banner of doing the greatest good for the greatest number. For this reason we justify imposing quarantine to prevent the spread of infectious illness. In the same spirit some scientists and regulators would ask patients who participate in medical research to make sacrifices for the greater good. Their position puts them at odds with the Declaration of Helsinki, which does not mince words in choosing between the greatest good for the greatest number and the rights of the individual patient: "In research on man, the interest of science and society should never take precedence over considerations related to the well being of the subject."[1] This ethical choice of the patient's rights over the good of society in general is now up for re-examination as the World Medical Association deliberates the next revision of the declaration.

Under pressure from the FDA

Why would the World Medical Association consider stepping back from its strong support for the rights of the patient? It is under pressure to do so from several critics,[2 3] notably the United States Food and Drug Administration. The Food and Drug Administration mandates many human experiments as part of the approval process for new therapies, and it requires most of these trials to include a placebo group, even if it has already approved one or more treatments for the same condition under study.[4] The Declaration of Helsinki explicitly forbids the use of a placebo group if an accepted treatment exists. In fact, the declaration, short though it is, makes this point twice: "The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods" and "In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method."[1]

Under these guidelines placebo comparisons are unethical if there is a demonstrably effective treatment. The Food and Drug Administration has offered scientific arguments to defend its requirement for placebo comparisons in such settings,[4 5] but these arguments are largely unconvincing.[6–9] The administration contends, for example, that a placebo group is needed to provide the benchmark from which the effect of a new treatment should be measured. For practitioners, however, the fundamental question in evaluating a new treatment is how it compares with the best available treatment, and not whether it is marginally better than an ineffective placebo.[10]

Defenders of placebo controls argue that a placebo comparison is preferable to an active agent because it is a fixed and reliable reference point.[11] In fact, however, the placebo effect itself varies greatly, not only with the condition being treated but also with the mental outlook of the patient.[12] According to the Food and Drug Administration, comparing new drugs with approved drugs without using a placebo anchor point can lead to approval of ineffective drugs.[4] Its worry is that even an already approved drug can be ineffective at times. Thus, a new drug with no effect could appear comparable with an approved drug that was ineffective in the setting of the new trial. This argument is based on a vicious circle: because the Food and Drug Administration does not require precise estimates of effect for a new drug, but only a "statistically significant" difference between a new drug and placebo, studies for drug approval are typically too small to estimate the effect of an approved drug with much precision.[7] The Food and Drug Administration argues that because of this uncertainty in measuring the effect of drugs it has already approved, it cannot use these drugs as comparators in studies of new drugs. But larger studies in the first place would solidify knowledge about the effects of approved drugs, reducing the uncertainty and negating the administration's argument .

Is the FDA trying to enforce an unethical position?

Putting science before ethics

The most glaring defect in the Food and Drug Administration's position is that scientific arguments, right or wrong, are placed ahead of ethical concerns. Unfortunately, the Food and Drug Administration has the muscle to live by its own rules. It can and does deny approval for drugs unless their effect is compared with placebo.[4] Its power is sufficient to coerce ethics committees to approve studies that would otherwise be rejected on ethical grounds.[13] Even so, the administration has adopted a strategy to overcome ethical objections to its policies, not by changing its policies but by changing the ethical standard, and revising the Declaration of Helsinki itself. In the January 2000 issue of the Hastings Center Report, Nicholson reported that at an international workshop to consider revisions to the declaration, "the only substantial support for rewriting came from some US participants.…Robert Temple, director of drug evaluation at the FDA, argued that the low risk to subjects justifies the use of placebo arms in clinical trials when effective treatments are available and equipoise is therefore impossible. But that puts the interests of society before the interests of the research subject, which is prohibited by the declaration, and the physician fails in his duty to do his best for the patient."[14] Indeed, apparently scant support was to be found at the conference for the viewpoint advanced by the Food and Drug Administration.

Informed consent by itself is not enough

Thus far the World Medical Association has not indicated any interest in weakening the declaration. We hope that it will maintain its resolve. The Food and Drug Administration and its supporters argued that placebo comparisons would be used only in situations in which the risks to patients were slight. Yet the underlying principle is that the researcher should be given zero latitude to decide how much additional risk or discomfort a patient should endure to satisfy the researcher's aims. This sharp boundary would protect society from rogue investigators and protect researchers themselves from self delusion when they weigh their research goals against risks to patients.

Strengthening the declaration

The Declaration of Helsinki was never intended to be immutable, and in fact it has already been revised several times. There are several issues that the World Medical Association might address to strengthen the declaration. We offer the following suggestions.

Declare that placebo comparisons are unethical

(1) The declaration already emphasises that the interests of society and science should concede to those of the individual. It should be revised to indicate that even small exceptions to this principle would open a hole in the dyke that would cripple the authority of the declaration. Thus, we propose that the revised declaration should offer some clear examples for more definitive guidance. It might suggest as one such example that even in studies of new analgesics to study relief from pain such as headache, the new remedies should be compared only with existing analgesics, and never with placebo. The example will reinforce the point that this principle is not a blurry boundary.

We note that the declaration does not prohibit healthy volunteers from subjecting themselves to risk for the benefits of science and humanity. It does, however, distinguish between a healthy volunteer and a patient, and the declaration is fussiest about the rights of patients. Thus, it would be ethical under the declaration for someone who currently does not have a headache to volunteer to receive either a new drug or a placebo on the next occurrence of a headache. The rules are different, however, for patients: it would not be ethical to enlist in an experiment someone who currently has a headache and wants relief from it if that experiment might involve assigning a placebo treatment for the headache.

Allow no discretion to investigators

(2) The declaration should assert its authority by stating that no investigator or regulatory official has the right to decide how much sacrifice in terms of risk or discomfort a patient should endure in the name of science.

Assert the importance of equipoise

(3) Equipoise is a state of genuine uncertainty about which of two or more treatments is preferable.[15] Without equipoise, investigators believe that one treatment is better or worse than others in an experiment, and thus they deliberately assign some patients to a treatment that they believe is inferior. We believe that equipoise is an essential ingredient of an ethical human experiment and that the declaration should say so. Still up for discussion is whether the state of genuine uncertainty can be reached collectively or must apply to each investigator in the trial.

Informed consent alone is not enough

(4) Some investigators believe that once informed consent is obtained little else matters. The declaration already emphasises the importance of informed consent, but it should be amended to state that informed consent by itself is not enough: the rest of the declaration still applies. The declaration should also emphasise that informed consent should be obtained using language readily comprehensible to patients, even uneducated patients, and it should describe all treatment options that would be available if the patient declines to participate.

A global, not a local, standard

(5) Perhaps the most difficult issue is whether a local or a global standard of reference should apply in regard

to what is the best accepted treatment. The controversy over the ethics of HIV trials in Africa revolves around this issue.[16] One rule might be that no one who enters a trial should receive a treatment that is worse than what he or she would have received in the absence of a trial. This rule applies a local standard. The alternative, a global standard, starts from the local standard but adds that no one who enters a trial should receive a treatment that is worse than what he or she would have received if the same trial were conducted anywhere else in the world at the same time.

There are good arguments for and against both points of view.[17–21] With the local standard a trial that is ethical in country A can be unethical in country B, a discomforting situation to some. On the other hand, attempting to apply a global standard may lead to an untenable escalation of the concept of the best possible treatment. Furthermore, the global standard may rule out pragmatic studies of innovative treatments that would be of use in countries that cannot afford expensive but proved treatments. The bottom line is that using a local standard may benefit participants and non-participants alike in impoverished countries, but it comes at the cost of using a double standard for what is considered ethical human experimentation. For this reason we favour applying a global standard.

Require public scrutiny

(6) Finally, we would like to see the declaration require that the design of all medical experiments should be open to public scrutiny. Currently many experiments conducted for regulatory approval are considered proprietary and kept from the public. The secrecy surrounding these studies makes it difficult, for example, to assess the extent to which the Food and Drug Administration supports or requires ethically questionable research by companies seeking approval for new drug applications. We think that the design and the results of these studies should be made publicly available. At the very least, even if the results are kept secret, the study designs should be made available for inspection.

Conclusion

We propose these revisions to strengthen what we believe is already a good document. The Declaration of Helsinki is intended to guide clinical investigators, institutional review boards, and journal editors to protect patients who become participants in medical research. Although we think the current version is clear with regard to the core principles, the message can and should be sharpened. We would like to see a strengthened declaration become universally acknowledged as the inviolable standard for ethical conduct of human experiments.—Kenneth J Rothman, Karin B Michels

Competing interests: None declared.

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Department of Surgery, University College London, London W1P 7LD

Michael Baum *professor emeritus of surgery and visiting professor of medical humanities*

AGAINST The transubstantiation from a professor of surgery to a professor of medical humanities might be considered a classic example of poacher turned gamekeeper. Yet as a lifetime proponent of clinical trials and evidence based medicine I have increasingly been persuaded that compassion and humanitarian values are best served by the scientific method rather than by a postmodern "impressionism." Rothman and Michels spit out the epithet "in the name of science" as if science was a neo-Nazi movement rather than a disciplined search for an objective reality in the service of mankind.

Like Rothman and Michels I resent the US Food and Drug Administration and its cultural and ethical imperialism. Paradoxically I also resent the bureaucracy involved in bringing clinical trials "up to Food and Drug Administration standards" in drug evaluation, which is intended to protect subjects in the trials but simply increases costs and delays the adoption or rejection of new therapies.

An Aunt Sally

As far as the placebo issue is concerned I believe Rothman and Michels are using the Food and Drug Administration as an Aunt Sally. I cannot believe that the administration would insist on a placebo control in trials of life threatening disorders for which there already exists a treatment that has a favourable effect on its clinical course. However, I instinctively reject absolutism and I can conjure up scenarios in that dreaded grey area of ethical relativism.

The authors insist on a single standard … What breathtaking presumption

Let's take the example of cyclical mastalgia. This is a common condition affecting up to 30% of young women in their reproductive years. It can be miserable but is not life threatening and has a very variable course. A placebo in this setting is not the same as no treatment because it can produce relief in many cases

through mechanisms we can only speculate on. Prolactin inhibitors are a specific remedy in most cases but at considerable costs in side effects and to the drug budget. I would therefore have no problem with a placebo controlled trial in this setting when a new putative cure pops up.

One standard for all?

Let us now consider the issue of the globalisation of standards. The authors insist on a single standard, taking discretion away from the hands of the researchers on the ground. What breathtaking presumption. What about the issues of appropriate technology and the developing world? Again let me illustrate this from an example in my own subject area of breast diseases.

Indraneel Mittra from the Tata Memorial Hospital in Mumbai and I are proposing a clinical trial of clinical breast examination versus mammographic screening for diagnosing breast cancer. Breast cancer in India presents at a later stage than in the United Kingdom or the United States, and a mammographic screening programme would have to compete with arguably more appropriate demands on scarce resources. Surely a trial of this nature in India is ethical and appropriate when it might be considered out of order in the rarefied atmosphere of Orange County, California?

Demanding zero risk and zero tolerance does not help

However, my main concern with Rothman and Michels' polemic is its antiscience stance. Perhaps that's because they are epidemiologists by persuasion, fluent in the observational methodologies but perhaps lacking in sympathy with us experimentalists. If a suspected murderer is on trial for his life, society demands the best possible evidence before convicting him or her. Surely if our patients are facing a life threatening disease they deserve the best possible evidence of therapeutic efficacy in their defence. Difficult though it may be, this evidence has to be garnered through the process of the randomised controlled trial—the expression of the scientific method in clinical medicine. The tensions between the conduct of a trial and the autonomy of the individual have been well rehearsed, and demanding zero risk and zero tolerance does not help the discussions.

No place for absolutism

These absolutist demands suggest a double standard when compared with the ad hoc nature of treatments outside of clinical trials. Also the spectre of the rogue investigator is irrelevant as the important clinical trials are always conducted by collaborative groups with more than enough safeguards from local and multicentre institutional review bodies. Finally, to state that "One rule might be that no one who enters a trial should receive a treatment that is worse than what he or she would have received in the absence of a trial" presupposes that we know the answer to the trial in advance. It could equally well be argued that those denied the opportunity to join the trial have a 50:50 chance of getting the worse treatment in any case.

Rothman and Michels start by claiming that the Declaration of Helsinki was never intended to be immutable but conclude by stating it should be inviolable. This subtle distinction escapes me. All such declarations, prescriptions, and codes of conduct have been the works of fallible human beings. It is a sign of maturity to reject the claims of the absolutists and accept that ethical dilemmas are dilemmas that cannot be solved by the rule book but have to be debated each on its own merits by scholars whose knowledge extends both BK and AK (before Kant and after Kant).—Michael Baum

Rothman and Michels' riposte

We shuddered to read Dr Baum's characterisation of our views as anti-science, "as if science were a neo-Nazi movement." Contrary to his implication, we are career scientists who not only esteem science but live it as an occupation and preoccupation; we even conduct experiments with human subjects. In ridiculing the spectre of neo-Nazi scientists, his ringing rhetoric is historically off-key: surely Dr Baum must know that the Declaration of Helsinki stems from the Nuremberg Code, which was written as a reaction to Nazi abuses. Science today is not a neo-Nazi movement, but Nazi science is precisely why we have an ethical code for human experiments.

Dr Baum calls us absolutists, and he claims that we "insist on a single (global) standard" of treatment, rather than a local standard of treatment. We didn't insist but wrote, "There are good arguments for and against both points of view" and then offered some arguments against adopting a global standard before suggesting why we favour one. Nevertheless, even Dr Baum must agree that there ought to be clear ethical boundaries for medical experimentation. Describing these boundaries should not be an ad hoc exercise in airy Kantian debate about every study. Indeed, there are some rules that you can live by.—Kenneth J Rothman, Karin B Michels

Endpiece

Dangers of anaesthesia, 1884

Relief from pain and suffering, when it can be accomplished with comparative ease and safety, must be regarded as a luxury. But like many luxuries [anaesthesia] has manifest disadvantages. Apart from any danger connected with the diminution or removal of pain, which is an essential part of a complicated natural process, it must not be forgotten that the inhalation of these stupefying vapours produces temporary havoc amongst the cells and fibres of the brain and their functions. The will being paralysed, words are spoken, and actions attempted which in a state of sensibility would never have been uttered or performed, no nor even contemplated. It may be positively affirmed that the involuntary and erratic emanations from the brain, whether in the form of words or actions, cannot be either edifying to the observer, or satisfactory to the patient.

Edward Thomas Tibbits, *Medical fashions in the nineteenth century*. London: HK Lewis, 1884:22.

Submitted by Ann Dally, Wellcome Institute for the History of Medicine, London