

The Misunderstood Placebo

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To put it simply, the World Medical Association Declaration of Helsinki is a mess. Section 29 of the recent Edinburgh revision states:

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.¹

The second sentence has survived from section II.3 of the 1996 Somerset West revision.² The first is a replacement of "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." The revision is regarded as having made it more difficult to give placebos in clinical trials and, therefore, to grant subjects more protection. It has been preceded, in recent years, by various criticisms of the use of placebos in medical research.³⁻⁵

The revision has made a badly worded paragraph worse. Contrary to what is implied, it is often *only* placebo-controlled research that is ethically acceptable. This is true even when an effective (or partially effective) remedy exists. It is often ethically unacceptable to test new remedies against "current prophylactic, diagnostic, and therapeutic methods," whether these are best or not. The kindest interpretation of the Edinburgh revision is that it is badly drafted. Defenders of it will claim that I am misinterpreting its intent. However, those who draft guidelines

that are meant to legislate for the behavior of others ought to pay more than a little care to the wording. A more cynical view as to how this statement came to appear in the Declaration of Helsinki is that those drafting it did not understand what they were discussing.

Some examples

To see why, let us consider a concrete example and take both a life-threatening disease and one for which some current therapy exists. Most would agree, I think, that AIDS fulfills the first condition, and many would accept that zidovudine fulfills the second. We have now had several therapeutic advances in treating patients infected with HIV and many of them have been developed in the era since zidovudine's acceptance as a (partially) effective treatment.

The table lists a selection—by no means complete—of clinical trials in HIV using zidovudine and run in the second half of the 1990s. All of the trials are placebo controlled, and five of them are specifically referred to as such in the abstracts or titles of the papers describing them.^{6,9-10,12-13} The purpose of the placebo is to blind these trials. This is really the *only* purpose of a placebo. One may note, by the by, that the following apply to placebos:

- They are specific to a treatment.
- They are nearly always necessary to blind a trial.

The second point is true even if two active treatments are compared because these treatments often differ in shape, size, and color. The double-dummy technique then has to be employed, and if different dosing schedules are used, then the

technique of dummy loading is necessary as well. This point would not be worth laboring but for the fact that some notable critics of the placebo do not appear to understand it.

None of the trials in the table compare the newer therapies *to* zidovudine. All of them compare an experimental therapy to placebo *in the presence of* zidovudine.

The CAESAR trial example.

Consider, for example, the CAESAR trial.¹² There were two arms of the trial, zidovudine plus lamivudine and zidovudine plus lamivudine placebo. The purpose of the trial was to compare lamivudine to no treatment. The fact that all subjects were treated with zidovudine was, presumably, accepted as an ethical constraint of the trial, but this trial was not *about* zidovudine. For example, if scientific curiosity were the only consideration in planning the trial, then, presumably, zidovudine would not have been included at all. If we read the Declaration of Helsinki, and if we take it at face value, then this trial is unethical. The exception allowing for the use of a placebo in the statement quoted above—namely that "where no proven prophylactic, diagnostic or therapeutic method exists"—does not apply. This statement was in the previous revision also. The new revision, however, requires that "The benefits, risks, burdens and effectiveness of a new method should be tested *against* [emphasis added by author] those of the best current prophylactic, diagnostic, and therapeutic methods." I would argue that in this trial lamivudine was not being tested against zidovudine and that therefore this trial would now fail the Helsinki test on this criterion as well.

Amendments to the Declaration of Helsinki "made a badly worded paragraph worse," says this professor.

Defenders of the declaration will argue that this criticism misses the point and that provided we define the experimental treatment as zidovudine plus lamivudine rather than lamivudine alone, then we can regard the comparator as being zidovudine rather than placebo. There are two objections to this. The first is the minor one that the wording would still seem to exclude the use of a placebo in this trial, although it is necessary to blind it. The second is the major criticism that the new wording would not only fail to exclude but would actually encourage a type of trial that many physicians would consider ethically unacceptable under the circumstances. Such a trial would have two groups, one given zidovudine and the other lamivudine (each, of course—if the trial were double blind—given with matching placebos to the other treatment). The unacceptable feature of such a trial would be that subjects on the experimental arm would be denied a therapy that had been added to the standard therapeutic armory and would be offered an as-yet-unproven therapy instead. Such a trial would have been much more difficult under the previous corresponding paragraph of the Declaration of Helsinki.

Thus the Declaration of Helsinki, in particular as now revised, does both too much and too little—too much in excluding placebos where the disease is serious and effective remedies exist, and too little in not protecting subjects entered into active control studies but denied the standard treatment (given an experimental one instead).

My opinion is at odds with one expressed by Rothman (a stern critic of the placebo). He states, “As medical knowledge accumulates, the number of placebo trials should fall.”⁴ On the contrary, as medical knowledge advances in some fields, it may be only add-on

Trial name	Year reported	Number of groups	Treatments
Protocol 241 ⁶	1996	2	zidovudine + didanosine + nevirapine zidovudine + didanosine + nevirapine placebo
INCAS ⁷	1997	3	zidovudine + nevirapine + didanosine placebo zidovudine + didanosine + nevirapine placebo zidovudine + didanosine + nevirapine
PENTA-4 ⁸	1998	2	NRTI + 3TC NRTI + 3TC placebo
Henry et al. ⁹ Study 193A	1998	4	zidovudine alternating monthly with didanosine zidovudine + zalcitabine zidovudine + didanosine zidovudine + didanosine + nevirapine
Florida et al. ¹⁰	1999	2	zidovudine + ddl + nevirapine zidovudine + ddl + nevirapine placebo
Been-Tiktak et al. ¹¹	1999	4	zidovudine + delavirdine low dose zidovudine + delavirdine medium dose zidovudine + delavirdine high dose zidovudine + delavirdine placebo
CAESAR ¹²	1999	2	zidovudine + lamivudine zidovudine + lamivudine placebo
AVANTI 1 ¹³	1999	2	zidovudine + lamivudine + loviride zidovudine + lamivudine + loviride placebo

trials that are acceptable. Such trials will give all subjects the standard treatment, but some will receive the experimental treatment in addition and some will receive placebo.

A hypothetical example.

Consider the case in which we already have a partially effective treatment (A) in use and wish to investigate a new treatment (B). The subjective probability that we assign to B being more effective than placebo (P) must be higher than the probability that we assign to its being better than A, since A is partially effective. It is much more plausible that the expected utility of B will be greater than P, even if both are given in the presence of A, than that the expected utility of B alone will be greater than that of A alone. After all, most drugs never make it to the market and most that do are not a success. It then follows that a trial comparing B to P in the presence of A (a placebo-controlled trial) could be ethical; but a trial comparing A and B might not be. Experienced drug developers know about this consideration and trialists

constantly face it. But the revised and misguided provision of the Declaration of Helsinki now encourages the trialist to compare A and B directly.

In fact, the ethical problems with placebos have been misunderstood. They are problems of consent and not of failed beneficence. This point will be taken up in due course.

Standard of care

I propose an alternative way of looking at ethics in clinical trials. This is to establish what a given patient's therapeutic entitlement is if the patient is outside the trial. Something of the sort is included in section 16 of the current Declaration of Helsinki, which includes the statement, “Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subjects or to others.”¹ That is, or should be, the cornerstone of the approach to ethics in clinical trials. The unstated implication—that research should not proceed unless this assessment justifies

it—will often, however, reveal as unethical the requirement it contradicts to test against “best current prophylactic, diagnostic, and therapeutic methods.” Ironically, placebo-controlled trials would be compatible with not harming the subject.

The patient's entitlement then becomes the standard of care against which a trial must be judged. This must then be followed by a risk-benefit assessment against this standard of the value to the patient of being entered into the trial. Generally, entry into a trial should only proceed if this assessment is positive or at worst neutral. For some less serious chronic diseases in which the subjects are willing to make a temporary sacrifice in the full knowledge that they are doing so, this requirement may be waived. The most vigorous critics of the placebo would not allow this waiver.

It is necessary to personalize this, however, to make it clear how absurd an absolute position on this would be. I suffer badly from hay fever and have done so for over 30 years. I often take

medication in the hay fever season but have also often tried doing without. The possibility of my being given placebo in a clinical trial for hay fever would not act as the slightest deterrent to my entering it, and I would dismiss as presumptuous meddling any attempts by arm-chair ethicists to prevent me from exercising my free will to do so.

I *would* be concerned about possible side effects from experimental treatments. If, for example, I were to participate in a multi-dose study, I would want reassuring that single-dose studies had been carried out first, that the pharmacokinetics of the drug

A new treatment generally becomes viable only when a placebo-controlled trial has proved successful.

were well defined, and that dosing schedules were appropriate.

Returning, however, to the case of serious and possibly life-threatening conditions: In assessing the value to a patient of entering a trial, we could consider two alternative forms of a principle. According to the strong principle, we can proceed if the *expected* benefit to the patient (expected by the physician enrolling the patient) is at least as great by entering the trial, whichever of the treatment arms the patient is assigned to. The weak principle simply requires that this expectation is not negative by virtue of entering the trial. This would permit us to average over all randomizations an expected loss on one arm with an expected gain on the other to see if it were positive (or at least non-negative). I do not consider, however, that the weak version of this principle is worth defending. In fact, even if only the strong principle is admitted as acceptable, trials are still possible.

Point of departure

Using this approach of assessing the relative risks and benefits of trial participation, the standard treatment defines a point of departure. Any treatment in a clinical trial can be defined with respect to standard treatment by considering one of four strategies: elimination, augmentation, maintenance, or substitution.

Elimination is always partial because in practice there are many effective treatments that we give patients and which we never consider eliminating in a clinical trial. For example, even in the original trials of zidovudine, subjects will have been given

treatments to combat opportunistic infections as they arose, whatever arm they were on. Similarly, they will not have been denied nursing care and appropriate diet.

Augmentation occurs when, as in the experimental arms of the trials in the table, an experimental treatment is added to standard care.

Maintenance is then the strategy to be used for the control treatment arm.

Substitution is actually a combination of elimination and augmentation.

A trial comparing a maintenance arm to a substitution arm—that is, an active control study—is the sort of trial that the critics of placebos and those who drafted the Edinburgh revision had in mind as an ethical alternative to placebo-controlled trials. As we have seen, however, it is precisely trials that use this approach that are frequently ethically questionable. Unless there is an extremely strong

presumption that the new treatment will be effective, it generally becomes viable only when a placebo-controlled trial has proved successful—that is, a trial comparing maintenance of the standard therapy with its augmentation with an experimental treatment and using a placebo purely to ensure that the comparison is double-blind. At that point, the question may arise as to whether a simpler treatment regimen might prove effective. If there is a hope of increased tolerability, it may become acceptable to run that sort of trial. Such trials have been run for example, in epilepsy, and it is possible that future AIDS research will involve trials to see whether simpler treatment is possible.

Equipose abandoned

In the context of drug development, comparing maintenance of the standard therapy with its augmentation with an experimental treatment also enables us to abandon the constantly violated supposed requirement for equipose. Experimental treatments are not freely available. They are not registered, and (depending on the country) that makes it either illegal or impractical for treating physicians to give such treatments to their patients except by entering them in clinical trials.

Now consider a trial of the add-on variety discussed above. All subjects receive standard therapy. Some receive an experimental therapy in addition, and some receive placebo. Provided that the physician hopes that the new treatment will provide a benefit, the strong principle is satisfied. Those who receive the standard therapy are no worse than they were outside the trial. There is the expectation that those who are on the experimental arm will benefit.

Equipose does not then become a point of departure for the trial. It is a possible point of

arrival. The trialists start with the hope that the new treatment will prove beneficial. If this condition is satisfied, and if subjects are not denied standard therapy, then there is at worst an expectation of no harm and at best an expectation of benefit for every patient entered into the trial. The physician who says, "I cannot enter any patients into this trial because I believe that the experimental treatment is superior and I am therefore not in equipose," condemns all those patients to receive the treatment believed inferior.¹⁴ If patients are entered in the trial, they have an even chance of receiving the treatment believed superior. The trial (or program of trials) continues until the point is reached at which society, as represented by a skeptical regulator, agrees that this hope has been realized, or the investigators accept that their hopes have been in vain. In the latter case, equipose is reached and the trial stops.

Justice and clinical trials

Some will argue that such a scenario is only possible because of a political system that requires regulation of pharmaceuticals and which is itself unethical. Why should physicians be forced to enter patients in clinical trials in order to give them the chance to have a new treatment that they hope will be superior, simply because these medicines are not yet registered?

There are two answers to this. The first is that the policy that drugs should become instantly freely available cannot in any case be maintained. It is a long road from drug research to drugs on the market. If we have a system without regulation, this does not mean that as soon as a molecule is first postulated as a treatment it will be instantly available to all patients. The early Medical Research Council trial of streptomycin (which was in short supply) in tuberculosis provides a case in

point.¹⁵ Practical necessity will mean that initially some will get it and some won't. This provides the opportunity for society to require that the introduction of drugs be evaluated rationally.

The second argument is that we need to abandon the myth that health care is a closed two-party system of physician and patient. A third party is involved, namely society. We can take a perspective similar to that of John Rawls in his *A Theory of Justice*.¹⁶ We need to act in a way that is in the interests of patients in something like Rawls' famous "original position" in which we are invited to consider how we wish society to

would prefer the second sort of society, based on scientific evaluation of medicine, to the first.

Although we may expect to have to make some sacrifice at the point of sickness, we can expect on average to have gained from the sacrifices of others because the general standard of care to which we will be entitled is likely to have improved. It is thus perfectly moral and rational for society to regulate drugs in such a way that this system acts in favor of patients who are well as well as those who are ill. Once a drug is registered, however, it becomes part of standard care and thus of the patient's entitle-

absence of placebos in a clinical trial is largely an ethical red herring, at least with respect to concerns about missed beneficence. The alternative ethical approach to trials is to ask not whether placebos are being given but whether patients are expected to be worse off by virtue of being entered into the trial.

Strangely enough, there is a very common use of placebo that is unethical and seems to have largely escaped the attention of commentators. This has to do with consent. The fact that patients expect no loss of benefit by entering a clinical trial does not alone make it ethical to enter them. We are still required to have their consent—not least because it is their good right to question the judgment of their physician. Thus, even if by entering them in a trial we might expect that they would suffer no loss and possibly gain, it will be unethical for us to treat them with placebo without their consent.

In a double-blind, randomized clinical trial, this can be handled by a process of mutually agreed deception.^{14,17} The physician explains to the patient what will happen and that neither will know whether the patient will receive the experimental treatment or its placebo. The patient can even be shown the protocol. I would argue that all trialists ought to conduct their trials in the hope (if not the expectation) that patients will try to understand as much as possible about the trial. Trialists should thus do everything reasonable in their power to improve consent.¹⁸

Many trials, however, also employ a *placebo run-in*.¹⁹ This is a period in which all subjects are given a placebo. In my opinion, this is unethical. It is clear that the standard of open protocol cannot be applied, since there is no purpose to giving a placebo if subjects know that they are receiving it. It is sometimes

argued that the subjects are not actually lied to. Be that as it may, the standard of "the truth, the whole truth, and nothing but the truth" is not adhered to.

Consider, for example, the Physician's Health Study, where, ironically, it was physicians themselves who were deceived, since they were the subjects.⁸ This trial employed a run-in period during which subjects were given placebo to beta-carotene without being informed that this was so. One account suggests this study as a model and describes strategies to help deceive subjects.²⁰

This strategy is not only unethical but is in any case of limited scientific value^{21–24} and should be abandoned by trialists.

Recommendations

My recommendations are that instead of trying to legislate which treatments can and cannot be used in clinical trials and under what circumstances, we should move to a system of practical ethics with the following principles.

- The standard of care to which patients are entitled when not entered into clinical trials should be regarded as the standard by which the feasibility of the trial is judged.
- Patients should not be entered into clinical trials if it involves them in an expected loss on any of the trial treatments compared with the standard they would get outside the trial, unless the disease is not serious, the loss is temporary, and it has been explained to patients that such a loss is involved.
- The trialist should always observe the fullest degree of consent practicable.¹⁸

Subject to these constraints, the technical matter of choosing the control group and the design of the trial should be left in the hands of the trialist, subject to approval from participating

Trialists should do everything reasonable in their power to improve consent.

be arranged without knowing what position in it we will hold. (In making this comparison, I am, of course, aware that Rawls' purpose is very different than mine here.)

Now consider ourselves in the original position. Do we want a society in which physicians simply back their hunches, however ill-founded, or one in which new treatments are introduced in a regulated manner, having been studied in controlled trials? If we opt for the latter solution, we have to accept that if we fall ill, our physician may not always have the power to recommend the treatment she or he believes (but does not know) to be best. Our only hope of getting such a treatment will be to enter a clinical trial. Of course, if we could, it would be in our own best interests to have society arranged so that medicines are strictly regulated unless and until we ourselves fall ill, at which point we might like our physician to be free to back his or her hunches. Such an attitude, however, is unethical.

It is quite plausible that we

ment. Such drugs, therefore, should not be withheld from clinical trial subjects in the interests of future patients unless, perhaps, the subjects participating in the trial are themselves potential future beneficiaries, as might be the case with certain chronic diseases.

I would argue that this general approach ought also to be implemented in areas in which the medical profession is largely self-regulating so that even if medicines were readily obtainable when untested, their introduction would be by careful study through clinical trials. This would require physicians to operate a self-denying ordinance in the interests of their future patients, in the knowledge that their current patients were now reaping the benefits that this attitude—through application to previous generations—had now acquired for them.

Informed consent and placebos

The preceding argument suggests that the presence or

physicians, ethics committees, and, of course, patients.

The Edinburgh revision of the Declaration of Helsinki may have been drafted with the best of intentions, but whether or not its authors were confused about their subject, the document they have produced is confusing. To follow it literally would be both unscientific and unethical. The ink is not dry, but already further revision is urgently needed if this declaration is to play any useful part in reducing the sum of disease-induced human misery.

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