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## RESEARCH ETHICS

## Consent to open label extension studies: some ethical issues

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A frequent feature of pharmaceutical research is the open label extension study, in which patients participating in double blind placebo controlled trials of new medications are invited, on completion of the initial trial, to take the study drug for some further period. Patients are openly given the active substance at this stage, regardless of their assignment in the initial trial. Investigators are typically reluctant to unblind the patients' assignment at the point of entry into the open label phase, on the grounds that this may introduce ascertainment bias in the main study.

It is argued that patients invited to participate in open label extension studies cannot give a proper consent to such research unless they know to which arm of the main trial they were recruited. It is further argued that to recruit certain groups of patients from placebo controlled trials into open label extension studies may also be unethical for clinical reasons.

Health care research rests in a delicate state of balance between the interests of society, the interests of the investigator, the interests of sponsors, and the interests of the research participant. Agreement or consent forms a key element in health care research. This includes agreement on the part of society that the conditions should exist in which research can and should take place, agreement on the part of investigators that they will conduct such research and conduct it according to some agreed standards of ethical conduct, and agreement on the part of participants that they will submit themselves to the procedures required in any given study. As Evans and Evans<sup>1</sup> point out, these broad groupings of interested parties can be subdivided into many smaller subgroups and these groups are not mutually exclusive. One consequence of this is that conflict of interest between the many groups is inevitable. Evans and Evans take it as read that of these interests, given that we cannot satisfy them all, we should be most concerned to protect those of the human research participant. They observe that this principle is so well established that they can "state it . . . without further justification and . . . assume its truth in all of what follows".<sup>2</sup> I doubt that many people would seriously challenge this position (I certainly have no intention of doing so here) although there is scope for debate about the precise nature and strength of those interests and what might constitute a serious threat to them.

My intention in this paper is to draw attention to, and illustrate with an example, a situation in health care research in which there is a danger of the principle of the primacy of the interests of those who volunteer to take part in research being subverted in favour of the interests of others, mainly of investigators and their sponsors but also, perhaps, of other sections of society. The situation I have in mind is the open label extension study, a relatively common type of drug trial. A recent MEDLINE search for "open label extension studies", limited by publication type to randomised controlled trials, produced 55 references between 1992 and 2000. Open label extension studies typically follow on from (and are hence an extension of) a double blind, placebo controlled trial of a new medication. Participants who complete the placebo controlled stage of the trial are invited to continue in the study for a further period, which may be quite extensive, during which time they will be given the investigational drug, regardless of which arm of the trial they had originally joined.

## AUTONOMY AND CONSENT

So much has been written about respect for the person, autonomy, and consent in recent years that it seems hardly necessary to expand much upon these concepts here. I will, however, briefly set out my starting assumptions. The first of these concerns a reluctance to be specific about what counts as a person. I will refer simply to research involving humans, on the assumption that all human beings involved in research have some moral status, are to a greater or lesser extent vulnerable, and deserve protection from the harms that may result from that research. To some extent I have sympathy in this regard with Gordijn's<sup>3</sup> argument that "it is perfectly possible to analyse bioethical problems concerning moral status without using the concept of the person or a somehow disposed substitute". I propose concerning myself only with competent adults as the primary concern of the paper, although I will make some brief references to those who are incompetent.

Autonomy is frequently presented as synonymous with respect for persons, but seems to fit the case as described by Gordijn, in that it is enough to ask whether autonomy is a morally relevant consideration in any given situation, for any given individual. One does not need to resolve disputes about the status of the personhood of a fetus, or of a patient in persistent vegetative state (PVS), to agree that neither is capable of autonomous action, but that both have moral significance. Many participants in research will be autonomous and thus their right freely to make decisions about the ways in which they dispose of their lives must be respected. Those for whom there is a question as to their autonomy will require special consideration and special protection. Autonomy is not, of course, a binary state that holds in every situation—in some situations I may be judged competent and in others I may not. Entry into a research project is one situation in which, for many reasons, even highly intelligent and well informed individuals may reach the limits of their competence. A key role for a research ethics committee must thus be to ensure that necessary safeguards are in place to minimise the likelihood of potential research participants unwittingly making unwise decisions.

As Evans and Evans point out: "a proper consent is a clear, open, intentional—and, we might usefully add, true—statement by the subject that he understands what he is about to do and that he freely chooses to do it".<sup>4</sup> As they go on to say,

this requires that the subject possesses and understands all the relevant information and makes his choice “freely, without pressure”.<sup>3</sup> They conclude that “without the consent—and without a clear means to securing it, freely and fairly, as an integral part of the research design—the REC cannot approve a piece of research as being ethically appropriate”.<sup>5</sup>

### PLACEBO CONTROLLED TRIALS

It is necessary to say something briefly about the general question of the use of placebo controls. The most recent revision of the Declaration of Helsinki<sup>6</sup> and, in particular, section 29, has given rise to a fresh debate about the ethics of placebo controls, given its recommendation that placebo should only be used when there is no proven effective treatment and, therefore, that where there are effective treatments available, trials should be comparisons of the new compound against the standard treatment. The Helsinki declaration has, of course, no statutory force in the UK. It is a set of guidelines and guidelines may not always be followed. Many treatments in common use are not necessarily “*proven* prophylactic, diagnostic or therapeutic” methods<sup>7</sup> (emphasis added). Investigators continue to argue that there are good, ethical, and scientific, grounds for using placebo in situations where the level of risk or discomfort is acceptable and the patient makes an informed decision to risk going without medication for the period of the trial—for example, Lewis *et al*, Kupfer *et al*, and Walsh *et al*.<sup>8–10</sup> I do not intend pursuing this argument any further in this paper. Concerns about the open label extension study following a placebo controlled trial will continue as long as there are placebo controlled trials.

### CASE STUDY

The following case study illustrates a situation in which the possibility of a proper consent becomes a central issue. In particular it raises questions about the extent to which the convenience of the researcher (and possibly, by extension, the concerns of society) can justifiably override the concerns of the individual research participant. The case is anonymised but is based on an amalgam of real examples.

The example, as suggested earlier, concerns open label extension studies to evaluate the safety and efficacy of investigational drugs, say, for the sake of illustration, a drug intended for the management of chronic pain from a neuropathy. In this design patients who have previously been enrolled in a randomised double blind placebo controlled trial are asked to consent to a further period of study for one year, during which they know they will all receive the study drug. The patients will know they have been in a trial of the new drug but they will not know which arm of the trial they were in and thus they will not know whether they were taking the investigational drug or a placebo. If they enter the extension study they may therefore either be continuing to take the study drug or they may start taking it for the first time, following a period on placebo. The investigators argue that it is not desirable or possible to unblind the patients’ allocation in the first study prior to their consent for the extension study because this would jeopardise the double blind design and allow the risk of ascertainment bias.<sup>11</sup>

### ETHICAL ISSUES

The example raises several questions. Clearly it is important to maintain the blinded nature of the trial until after the data have been analysed and reported, for all the same reasons that the double blind randomised control trial design was adopted in the first place. It is, however, possible to break the code for any participant at any time and unblind that patient, in the event of an emergency or an adverse event.

Patients are recruited to trials and begin treatment one by one, over a period of several weeks or months and each will thus have different start and completion dates. Patients will therefore also approach the open label extension study one by one. Thus the dangers of unblinding will apply until the last patient completes the trial, the data have been analysed and the report written. But each patient, one by one, must decide whether or not to enter the extension study at the point at which she completes her involvement in the first part of the trial. The requirement for a valid consent is that the participant is in possession of, and understands, all relevant information to make their decision freely and fairly. The one piece of information the participant will not be given—must not be given, if one accepts the arguments of the investigators—is whether she has been taking active medication during the first part of the trial or whether she has been taking placebo.

It could be argued, however, that this is the one piece of information, over and above what the participant will already know from the information given at the time of recruitment to the previous trial, that is relevant and necessary for a proper consent. Consider the options:

1. The participant was receiving active medication
  2. The participant was receiving placebo
- A. The participant received good relief of symptoms with minimal side effects
- B. The participant did not receive good relief of symptoms and/or had unpleasant side effects

These can, of course, be combined as 1A, 1B, 2A, or 2B.

For participants considering entering the extension study, it would seem to be in their interests to know into which of these categories they fall. If a participant knew that she was in group 1A, taking active drug and getting good pain relief, she is likely to wish to enter the extension study. If a participant experienced 1B, taking active drug with poor relief, it would be in her interests to leave the trial and try one of the other medications available to treat this condition. Participants who fall into 2A are in an interesting position. They have achieved good symptom relief without active medication, either through the power (if there is such a thing) of placebo or because they are in spontaneous remission. Is it appropriate to recruit someone who may have no further need of medication and start them on a year’s course of an experimental drug? Not knowing they were taking placebo and finding their symptoms relieved these participants might enter the extension study in the belief that they must have in fact be in 1A and this is their best option for continued symptom relief. Participants in 2B have a straight gamble: if they think they were taking active medication they will refuse the extension study, but if they think they must have been taking placebo they might well decide to enter the study in the hope that the active drug will work for them.

When trial participants are first recruited to randomised controlled trials (RCTs) they are told about the randomisation process and that the use of a placebo involves some patients being given a dummy pill, which may be expected to have no effect. It is made quite clear that chance is at work and no one can know which arm of the trial they will enter. This element of chance is a necessary component of the trial method and is justified in the interests of good science. When the study becomes an open label one, however, it is difficult to see any justification, in the context of the new study, for keeping up the concealment. The questions being addressed by the extension study concern long term efficacy and safety, gaining experience of using the drug over a longer period of time in the real clinical world, and the participants, by definition, know what they are taking.

The only apparent justification for not giving patients the information they require seems to be the convenience of the

investigators. They have ready access to a group of people who have already shown themselves willing to take part in research. If they waited until the first study was completed and the data analysed they might have greater problems, and incur greater expense, recruiting a sample from scratch. If they wish to take advantage of their contact with the study sample but were obliged to unblind participants before recruiting them to the open label extension they would have to arrange things so that the data collection and analysis for patients in the double blind trial was carried out by one team of people, while recruitment to the extension study was done by someone else. Thus the refusal to unblind each patient prior to inviting their participation in the extension trial looks primarily as if it were intended to make life easier for the investigator. Making life easy for investigators is not necessarily a bad thing, of course, but it should not be achieved in ways contrary to the interests of the study participants.

It might be argued that there is scientific merit in not unblinding participants before their enrolment in the open label study. In an ideal trial one might imagine, at the end of the double blind comparison phase, those participants who received active treatment showing a good improvement in their condition, while those receiving placebo would show little or no improvement. At the end of the open label extension phase the participants in the active treatment group would continue to show good results, and those in the placebo group would also achieve good results, comparable to those who had been receiving active treatment all along. The open label phase, following the double blind phase in this way but maintaining ignorance of which arm of the trial the patient had been in, would thus add useful weight to the evidence for the therapeutic benefit of the new drug. By not revealing to patients the fact that they were in the placebo group any risk that this knowledge and the knowledge that they were now about to receive the real thing would lead to a psychological benefit, would be minimised.

This would seem, however, to suggest a lack of confidence in the placebo controlled randomised controlled trial as a research design. The whole point of such an experiment is to argue that the experimental drug has a therapeutic benefit that exceeds the effect of a placebo. At the end of the double blind phase we should have the data that tells us how effective the drug might be, compared to placebo and if the RCT design is fit for purpose that should be sufficient.

Open label studies are defended on the grounds that they provide valuable "real world" experience of the use of a product, and are more about efficacy than theoretical effectiveness. Patients in the real world come to therapies with all manner of predisposing and confounding factors at work in their clinical make up. If the open label extension is to give meaningful experience of real life clinical use there would seem to be little justification for not unblinding participants before they enter such trials and it is of course open to patients to offer their services to the investigators regardless of which arm of the trial they discover themselves to have been in. But proper consent to the open label extension study would seem to require that patients have knowledge of what treatment they have been taking.

As suggested earlier, there is a particular concern for patients who received placebo in the original trial and whose symptoms have disappeared. Doubts have recently been expressed as to whether there is actually any such thing as a placebo effect<sup>12</sup> and while the debate may be unresolved, there is no doubt that many patients simply get better with no treatment. For patients in the placebo arm of trials who report good relief of symptoms (which in studies of depression, for example, may average 50%<sup>13</sup>) it would seem wholly inappropriate to administer a pharmacologically active substance for a further lengthy period when there would appear to be no clinical grounds for its use. Inclusion criteria for the double blind phase of the trial would normally require that

participants suffer from the study condition or show the symptoms for which the study drug is said to be a treatment: spontaneous remission or recovery during a placebo phase of treatment would seem to represent good grounds for exclusion from any further participation in the study. This argument leads us then to consider that some patients in the active treatment arm of the first study may also no longer require medication and so their continued treatment may also be questionable.

Two further points are worth brief discussion. The first concerns the fact that, in the author's experience, the patient information sheet for the main study usually mentions the possibility of inclusion in an open label extension study at the end of the first phase of the trial. This may constitute an inducement or a form of coercion to persuade patients to volunteer for the trial. If, for example, there is no currently accepted treatment for their condition, or if the treatments they have tried to date have not been effective, the gamble that they might receive placebo for a relatively short period may be more than offset by the knowledge that they can then be sure of receiving the new treatment at the end of the study. This incentive will be even greater when the study involves a drug not yet licensed for that particular application, or that may not be funded by the relevant health care services.

The second concern, which follows in part from the first, is that patients may be very likely to be keen to enter the open label phase of the study, for the very reasons suggested above. As I have suggested, however, for a proportion of patients this may in fact potentially be detrimental to their interests.

One possible solution to at least some of the problems might be to ensure that consent to the open label phase is not sought until completion of the double blind phase, and that at this time participants receive a specific information sheet, which emphasises the fact that neither the participant nor the recruiting researcher knows which arm of the trial the patient has been in, that any change in the patient's condition may not have been caused by the study drug, and so on. This would seem, however, still to present ethical problems. For one thing, the eagerness of patients to receive a new drug may well counteract any cautions of this type. Macklin<sup>14</sup> refers to patients falling prey to the "therapeutic misconception" which, she says, is "the all too common assumption that research promises beneficial treatment, even in its early phases". She goes on to report that:

In one study, people who had been research subjects told interviewers that they had trusted their doctors, believed that their physicians would do nothing to harm them, and thought that the physician researchers had always acted in their best medical interests. The misconception that research is designed to benefit the patients who are the subjects is difficult to dispel.

In the light of such faith a paragraph in the information sheet is unlikely to be sufficient to dissuade patients from entering the open label phase. In any event, as has already been observed, some patients who entered the double blind phase may, by the end of the study, no longer meet the inclusion criteria for the trial. The onus would seem to be on the researcher to establish their clinical suitability for continued treatment, rather than saying, in effect, that no one knows whether a patient needs or will respond to the trial drug but that the patient is never the less invited to take it for a year.

### INCOMPETENT PATIENTS

The discussion so far has concentrated on competent adult patients. There is the further question of incompetent patients, who may be entered into double blind placebo controlled trials where this is justified—for example, because



the research is of sufficient importance, could not be carried out on competent patients, and is directly concerned with the condition from which the patient is suffering. It would seem that, where patients are unable to give consent, it must be essential that the researchers have the patients' best interests as their first concern. It must be therefore even more important that, firstly, the open label study as a whole is ethically defensible on the grounds that the data will help to answer important questions. But further, it would seem essential that investigators unblind such patients and decide whether or not to enter them into the open label study in the light of the evidence from the first phase of the trial. It might be acceptable for a competent adult to volunteer to take an unnecessary drug for the sake of generating long term safety data. It would be unacceptable to gather similar data from incompetent patients.

## CONCLUSION

In conclusion, I have argued that consent to take part in research requires that potential recruits be given the information relevant to that consent, and that for open label extension studies that information necessarily includes knowledge of which arm of the original trial the patient had been in. I have further argued that investigators have a duty to unblind participants before recruiting them to the open label extension study on the grounds that administration of an active study drug to a patient whose condition has resolved spontaneously during the placebo phase of the study is also unethical. Practically speaking this should not present insuperable difficulties. All that is required is that recruitment to the open label extension study is managed by some individual not involved in the main study. This individual would have access to the study codes, would meet with patients on completion of the first phase of the study, tell them which arm of the trial they had been in, explain the implications of this and then, if they still meet the inclusion criteria

for the trial, invite them to join the extension study. For added security it might be wise to ensure that monitoring and data collection for the extension study is also handled by individuals not involved in the first phase, at least until that phase has finished. This may, however, be unnecessary: if it is acceptable for the same research team to run both the double blind phase and the open label phase it must also be thought acceptable for these researchers to have access to the data from the open label study while still conducting the double blind trial, so if there is a risk of ascertainment bias it must already exist.

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