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RESEARCH ETHICS

Consent to open label extension studies: some ethical issues

P Wainwright

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.

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 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”.

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 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 many people would seriously challenge this position (I certainly have no intention of doing so here) although there is some possibility of a person being autonomous (as defined) and of research participants being autonomous (as defined) and of research participants being competent. It is reasonable to suppose that many people have some moral status, are to a greater or lesser extent vulnerable, and deserve protection from the harms that may result from research.

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 investigator, the interests of sponsors, and the interests of research participants 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 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.
this requires that the subject possesses and understands all the relevant information and makes his choice "freely, without pressure". 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".

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 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 (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.
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 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.

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 prima facie as if 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 movement. At the end of the 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 patient needs or will respond to the trial drug but that the 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 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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5 See reference 1: 79.
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