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Clinical Research upon Mentally Ill Subjects Who Cannot Give Informed Consent

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The Problem

Over the last two decades increasing attention has been paid to the rights and safety of the subjects of clinical research. A key safeguard against any abuse has been the requirement to obtain the subject's informed, valid or true consent, which has been defined by the Medical Research Council as 'consent freely given with proper understanding of the nature and consequences of what is proposed' (M.R.C., 1962–3). However, it has been recognized by the M.R.C. that it may not be possible to obtain such consent from, among others, some subjects who are mentally ill. Whether or not a research project should be carried out on such subjects should depend, they say, on whether or not 'there are reasonable grounds for believing that a particular new procedure will contribute to the benefit of that particular patient . . .', and further, 'when true consent cannot be obtained, procedures which are of no direct benefit and which might carry a risk of harm to the subject should not be undertaken' (M.R.C., 1962–3).

Unfortunately this distinction between beneficial and non-beneficial experimental procedures is not easy to make. It is not sufficient to say that a beneficial result is intended, since this glosses over the element of doubt which is always present in any procedure which is new and experimental, however good the theoretical reasons may be for expecting a beneficial outcome. This is indeed widely recognized, so that the informed consent of subjects is now required as a safeguard in all clinical experiments, including those in which clinical benefit is hoped for (Declaration of Helsinki, *World Medical Journal*, 1976). The investigator's responsibility thus consists of weighing the risks and benefits and of explaining them to the subject; he must also carry out the experimental procedures with due care. On the other hand, it is the subject's responsibility to decide whether or not to participate, in the light of the information given to him on possible risks, discomforts, precautions and benefits.

What then of subjects who are unable to understand the nature of the risks and benefits? Can anyone else give consent instead? It is certainly wrong to assume that consent is not required, for this would mean reducing safeguards in experimental procedures on subjects who are among the most vulnerable. In law in the United Kingdom consent by others for the subject is allowed (a) only for experimental procedures leading to possible benefit, and (b) only by the parents of subjects under the age of 12 or by a legal guardian. There is thus no way in law whereby consent to a possibly beneficial experimental procedure can be obtained for a subject who is unable to give consent himself and who has no legal guardian and is not a child. In such cases even the nearest relative cannot legally give consent.

This gap in the law is probably not generally recognized. It can cause considerable difficulties in experimental procedures with severely ill and handicapped psychiatric subjects, as illustrated in the following account of the ethical aspects of a recent drug trial (Pryce and Gray, 1978).

The Piracetam Trial

(i) *Proposals*

Piracetam (2-pyrrolidone acetamide) is reputed to enhance the transfer of information across the corpus callosum (Buresova and Bures, 1976). Since an impairment of transcallosal conduction had been reported in chronic schizophrenia (Rosenthal and Bigelow, 1972; Beaumont and Dimond, 1973) the

investigators were interested in establishing whether Piracetam would be of benefit in this condition. There were no reports of its systematic use in schizophrenia, but the drug appeared to be virtually non-toxic. It was proposed to give it in addition to drugs currently being taken (mainly phenothiazines) to prevent the likelihood that some subjects would relapse if maintenance therapy were withdrawn (Leff, 1972). This was judged to be a more likely risk than any effects due to drug interaction. It was recognized that Piracetam might fail to produce clinical improvement or at worst might cause deterioration, and that subjects would inevitably be put to some inconvenience by being asked to take eight large white tablets daily in addition to their usual medication. In the proposed double-blind cross-over comparison between Piracetam and placebo any subject who showed any possible ill-effects would be withdrawn.

The Division of Psychiatry Ethics Committee, which did not have a lay member, approved the protocol of the proposed trial, but were concerned that some subjects would probably be unable to understand what was intended and therefore could not give true consent. In such cases it was agreed that consent should be sought from the nearest relative, or failing that from the chairman of the Ethics Committee acting *in loco parentis*, and that the relatives of those who could give valid consent would also be informed. The protocol was then referred to the Joint Ethics Committee (formed by the South Glamorgan Health Authority and the Welsh National School of Medicine), which included several non-medical members, and was approved.

(ii) *Practice*

Thirty-two men and 18 women in hospital with chronic schizophrenia were given a standard explanation of the nature of the trial. It was judged that a quarter, 6 men and 6 women, gave true consent, 5 men and 4 women refused consent (some for delusional reasons) and 29 subjects seemed unable to understand the explanation given. Seven of those who gave true consent were eventually included in the trial, of whom 6 proved to be only moderately handicapped on the Wing Sympton Scale (1961).

Replies to a detailed explanatory letter were obtained from the relatives of 17 of the 29 subjects who could not make a decision, all except two of the replies giving consent, some with expressions of interest and approval because something new was being tried. Two relatives refused, one because she did not wish to prejudice the patient's present state of improvement, and the other after a period of painful doubts as to whether she should give consent or not. The chairman of the Ethics Committee gave approval for the inclusion of 6 patients whose relatives could not be found.

There was no evidence of any ill-effects to the 27 subjects who eventually completed the ten-week trial, nor was there any apparent benefit from the drug.

Discussion and Proposals

There is a large area of clinical research on subjects suffering from psychiatric illness where ethical problems hardly arise. For instance, few problems are posed in comparative studies on different populations in which psychological and sociological measuring techniques are applied. Ethical questions arise when subjects are deliberately exposed during an experimental procedure to changes in their internal or external milieu which carry an element of risk. In most cases the risk can be explained to each subject, as well as the proposed safeguards and potential gains, so that the subject can decide for himself whether the risk is acceptable or not. There are occasions, however, as in the Piracetam trial, in which subjects are unable because of their illness to understand what the risks, safeguards or possible benefits are.

The safest thing for the investigator is to avoid such research on psychiatric subjects who are unable to give true consent, since consent given by others, even by a devoted relative, is not valid in law. In conditions such as schizophrenia this would limit research to milder cases, i.e. to those likely to be able to give true consent, and for many purposes this might well be sufficient to provide the answers required. Indeed, if answers could be so obtained, it would be wrong to include subjects who could

not consent. It is unlikely, however, that the public would wish to see research entirely limited to the milder cases of serious psychiatric illness, since the subjects of severe illness are precisely those whose therapeutic need is greatest, and the possibility of therapeutic advance may at times require their participation in experimental procedures.

Is it then possible to devise other safeguards comparable to the true consent of the subject? I believe it is, by taking into account that true consent is a lay decision, which does not require, as seems to be suggested by the M.R.C. (1962–3), an expert knowledge of the research techniques to be used. (Such knowledge, of course, is required initially to estimate feasibility and the probability of benefit and risk.) It follows that if informed consent is a lay decision, in its absence responsible laymen might reasonably be asked to act for the subject. There are at least two ways in which this might be done.

Gostin (1975) has suggested the establishment of 'The Committee on the Rights and Responsibilities of Staff and Residents of Psychiatric Hospitals' in each Region. One function of this review body, which might be set up by the Lord Chancellor, would be to consider 'treatment involving . . . the use of experimental drugs or other experimental treatments'. It is not clear how this body would link with existing Ethical Committees, but it would seem an appropriate arbiter on experimentation on psychiatric subjects who cannot give informed consent. The 'advocate' whom Gostin also proposes could also act for each subject who had no close relative. These proposals, however, are fairly radical and intended to cover a wide range of ethical problems in psychiatric hospitals. An alternative which would be easier to implement is to strengthen the lay membership and responsibilities of existing Ethical Committees. For instance, the Danish Medical Association, in implementing the recommendations of the World Medical Association's Helsinki Declaration II, is establishing independent Ethical Committees consisting of 'scientists and citizen representatives' on an equal basis (Riis, 1977). It would be reasonable, therefore, to expect that clinical research on psychiatric subjects who are unable to give true consent should be appraised by Ethical Committees consisting of equal numbers of laymen and doctors. In addition, the informed consent of a 'lay advocate' should be obtained for each subject who is unable to decide for himself. Normally this person would be a near relative, or failing that a lay person appointed by the Ethical Committee. This again would be in line with 'Basic Principle' 11 of the Helsinki Declaration II, which states 'where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation'.

Either of these suggestions would give better protection to both subject and investigator than is available now in this uncharted legal territory. Eventually, however, steps should be taken to close the gap in the law.

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