

Ethics of volunteer research: the role of new EC guidelines

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Introduction

Clinical research and drug development are crucially dependent on a continuing flow of willing volunteers. Large numbers of healthy volunteers, and patients with a variety of illnesses, are studied in the development of new drugs, the majority with the support of the pharmaceutical industry. Healthy volunteers are usually the first humans to receive a new agent, whereas patient volunteers are studied in the assessment of efficacy of drug therapy, as well as in pharmacokinetic and tolerance studies from which they are unlikely to gain therapeutic benefit. Although there is some debate about the need for healthy volunteer studies in drug development, for practical reasons such studies are likely to continue for early phase clinical trials. In the UK, in 1987, drugs were administered to more than 8000 healthy human volunteers of whom 3 (0.04%) suffered potentially life threatening adverse effects. Forty-five volunteers (0.55%) suffered moderately severe, but not life threatening, adverse events, and minor events (not requiring medical intervention) were reported in 565 (6.9%) volunteers (Orme *et al.*, 1989). Academic research employs additional human volunteers in studies that do not involve the administration of novel pharmaceutical agents. These, however, may not be without potential risk (Editorial, 1991). Due to the importance of continued clinical research, it is essential that society maintains its trust in the behaviour of those who study human subjects. If not, increasing legal restrictions may be placed on the use of human subjects and the flow of volunteers for such studies may decline. Indeed, there is evidence that this has occurred in several countries, most notably in New Zealand following revelations of unethical and poorly conducted clinical research (Gillet, 1990). As a further consequence, the charitable funding of medical research may suffer.

Adherence to a high quality code of ethics is essential. It is the only way in which the community can retain confidence in the integrity of clinical research. This adherence to high ethical standards can be maintained via self-regulation (by industry or profession), non-statutory government guidelines or legislation. Since the

1960s, a number of reports have been prepared by the medical profession and the pharmaceutical industry with the aim of improving, by self-regulation, the ethics of research in humans (Association of the British Pharmaceutical Industry, 1970; Medical Research Council, 1963; Royal College of Physicians, 1986, 1990a, b; World Health Organisation, 1982). It is now, however, becoming common for trials involving human subjects to be regulated either by law, as in France (Ministry of Health-France, 1990), or by non-statutory governmental guidelines as in Germany (Ministry of Health-Germany, 1988). This is partly due to a perception among governments that self-regulation is inappropriate, but is also due to the advent of the Single European Act in 1992 (Single European Act, 1986), and the drive towards a common European approach to licensing requirements for novel drugs.

The European Community (EC) has proposed setting up a central system whereby drugs may be licensed for the EC as a whole (European Commission, 1989; Smith, 1990). This system would be compulsory only for products derived from biotechnology, although companies could voluntarily submit other drugs as an alternative to using national regulatory agencies. The European licence requirements will not only specify the data necessary to show that a drug is safe and efficacious, but also include Good Clinical Practice (GCP) guidelines to prevent dangerously obtained or false data being submitted. Guidelines have been drawn up by the EC Committee for Proprietary Medicinal Products following extensive consultation with interested parties (European Commission, 1990). Despite the fact that these guidelines have arisen in order to regulate commerce, academic units should be aware of the proposals, as it is hoped that they will be applied more widely. All medical researchers, both within and without the pharmaceutical industry, should be aware of ethical issues relating to their work, of the impact of the proposed EC GCP guidelines, and of any areas inadequately covered by the guidelines.

Before these guidelines were formulated, there were several ethical issues concerning human subjects in

clinical trials (hereafter referred to as trials) where guidance was inadequate or inconsistent between countries. These include the role and composition of Ethical Review Committees (ERCs), the ideal method of obtaining informed consent, the role of the family doctor, the risk of over-frequent participation in trials, and the arrangements for subject compensation after adverse events.

EC good clinical practice (GCP) guidelines

These guidelines were first issued in draft form in 1988, and have since been revised on several occasions. A final draft was approved by the EC Committee for Proprietary Medicinal Products in May 1990 (European Commission, 1990). Their aims are to provide full protection for trial subjects, to improve the scientific quality of such trials, to establish the credibility of data obtained, and to ensure that data collected conform to international regulatory requirements. They also provide a basis for discussions between sponsor, investigator and the regulatory authorities. To these ends, guidance is given on the protection of volunteers (covering the role of ERCs and subject consent), the responsibilities of various parties (sponsor, monitor and investigator), data handling and quality control. There is a declaration from the outset that the personal welfare of subjects is a prime objective in any trial. This must be the ultimate responsibility of the investigator, who should know and follow the current revision of the Declaration of Helsinki (World Medical Association, 1989).

Subject protection

Ethical review committees Until recently there were wide variations in the legal status of ERCs. Some European countries, such as France, have recently set up statutory committees to review human research (Ministry of Health-France, 1990), whereas the UK and Germany rely upon non-statutory guidelines to ensure vetting by an ERC (Department of Health and Social Security-UK, 1975; Ministry of Health-Germany, 1988). The new French law on 'protection of persons undergoing biomedical research' stipulates that ERCs must be set up in every region, with membership including appropriate non-medical professionals capable of dealing with ethical, social, psychological and legal issues, funded by a fixed fee for each submission (Ministry of Health-France, 1990). The Minister of Health should be sent any submissions rejected by the ERC, and must also be notified separately of all proposed trials, which the minister may veto at any time. The French guidelines do not, however, cover the communication of protocol amendments and adverse reactions, or the provision of interim and final reports of trials, to ERCs.

The Department of Health in the UK has recently drafted new guidelines (Department of Health-UK, 1991). These state that all districts should have an ERC whose membership must include two lay members, at least one of whom should be unconnected to the institution, and one of whom should be chairman or vice-chairman. It is advised that protocol amendments

and adverse reactions should be referred back to ERCs. ERCs will be able to charge a small handling fee for commercially sponsored research. In addition, they advise indemnity for the legal liability of ERC members in the event of court action.

The new EC GCP proposals give coherent guidance on the role of ERCs. They make it clear that a trial must be approved before subjects are recruited, and that the information available to the ERC should amount to more than just the trial protocol. Additional material should include the investigator's curriculum vitae, details of the trial facility and supporting staff, subject information/consent sheets, the provisions for subject compensation, and the rewards made both to the subject and investigator. It is stressed that in its consideration of a study, an ERC should not merely consider the mechanisms for subject protection, but also the ability of the study to reach sound conclusions with minimal risk to the subject. In addition, the guidelines emphasise that the ERC must be informed of all protocol amendments, and of serious or unexpected adverse events occurring during a trial. The guidelines make clear that the names and positions of members of an ERC should be publicly available, as should its working practices (including response times). It is also suggested that ERCs should be so constituted that study proposals can be objectively and impartially reviewed independent of the sponsor, investigator, and relevant authorities. This would imply at the very least, that these parties could not be voting members of an ERC during consideration of their protocols, and at the extreme, that they should not attend, even as observers.

There are several issues which the EC GCP guidelines do not cover. The provision of interim and final trial reports to the ERC is not included, although review of on-going studies can be requested by the investigator. In contrast to the recent UK and French proposals, the guidelines give no detailed suggestions on the number or type of lay members, apart from stating that they should be included. It also seems to imply that nurses and paramedical staff represent the lay public. The EC GCP guidelines make no recommendations regarding the funding of ERCs. A further point of concern is the lack of guidance to ERC members on their legal liability, if sued because of adverse events in a study they had approved.

Subject consent Consent is an area where inconsistencies persist. Despite many reports and recommendations, it seems that some investigators fail to inform subjects adequately of the material facts relevant to a study (Gillet, 1990). Under these circumstances true 'consent' cannot be achieved. A properly constructed written consent form is generally preferred (Royal College of Physicians, 1986, 1990), completed either by the subject, or by an independent witness. This indicates that the consent is based on information which has been understood, and that the subject has freely chosen to participate without prejudice to legal and ethical rights, while allowing the possibility of withdrawal from the trial without having to give any reason. Some investigators do not obtain consent in this form (Orme *et al.*, 1989), particularly when patients are involved, and in non-commercial studies. Other areas which have not been

addressed previously include consent to personal information being disclosed to other agencies, and the need to update volunteers on new information pertinent to the drug, so that consent remains informed.

The EC GCP guidelines state that a subject be given a comprehensive explanation of the study, including an assessment of risks in relation to benefits. They also state that, where possible, subjects should be given written information in addition to an oral explanation. This explanation is expected to include details of the procedures for compensation in the event of adverse reactions. Although oral consent independently witnessed is permissible, written consent is preferred, and is considered mandatory in non-therapeutic studies. When the subject is unable to give consent, due to unconsciousness or mental illness/disability, trials can still take place if a legally valid representative gives consent, and if the ERC agrees to this arrangement. The investigator is held responsible for providing any relevant information which becomes available on the study drug during a trial. Subjects should be aware that personal information may be scrutinised during audit of a trial, and may be disclosed to the Regulatory Authorities.

Table 1 Sponsor responsibilities

1. To establish detailed Standard Operating Procedures to comply with GCP.
2. To agree a protocol, and all amendments, and the means of data recording with the investigator.
3. To select a suitably qualified investigator, with appropriate facilities, and to obtain agreement to compliance with the protocol according to GCP.
4. To provide the investigator with all relevant drug information before, or arising during, the study.
5. To provide the ERC and, where appropriate, the relevant authorities, with all necessary documentation before, and information arising during, the study.
6. To provide suitable investigational medicinal products, adequately packaged and labelled (e.g. for blinding), with appropriate quality control and records, and to ensure that the investigator has a system for their safe handling, storage and use.
7. To ensure that all monitors and support staff are appropriately trained.
8. To appoint appropriate individuals/committees to ensure satisfactory supervision and data handling to allow completion of the trial.
9. To consider promptly all serious adverse events, taking all measures to safeguard trial subjects, and to meet the reporting requirements of the appropriate authorities.
10. To inform the investigator, and to ensure notification of the ERC, promptly of any information immediately relevant to the trial.
11. To ensure preparation of a comprehensive final report of the trial, whether completed or not.
12. To provide adequate compensation/treatment for subjects in the event of trial related injury or death, and indemnity for the investigator, except for claims resulting from malpractice and/or negligence.
13. To agree responsibilities for data processing and statistics, report of results, and publication policy.

(Adapted from the Guidelines on Good Clinical Practice (European Commission, 1990)).

Table 2 Monitor responsibilities

1. To ensure adherence to the protocol and GCP, through working to Standard Operating Procedures in visits to the investigator throughout the trial period.
2. To ensure adequate trial site facilities, and availability of suitable subjects.
3. To ensure that the investigator's support staff are adequately informed, and comply with the protocol and GCP.
4. To check that informed consent has been obtained and recorded from all subjects.
5. To ensure prompt communication between the investigator and sponsor.
6. To check the case record form entries with the source documents.
7. To check that the storage, dispensing, return and documentation of investigational medicinal products are safe and in accordance with local regulations.
8. To assist the investigator in any notification/application procedures.
9. To assist the investigator in reporting of trial data and results to the sponsor.
10. To maintain a written record of all contacts and discussions with the investigator.

(Adapted from the Guidelines on Good Clinical Practice (European Commission, 1990))

Responsibilities

The EC GCP guidelines specify detailed responsibilities for the sponsor (pharmaceutical company), monitor (person appointed by the sponsor to oversee a clinical trial), and investigator. These responsibilities are detailed elsewhere (Tables 1, 2, 3). Important responsibilities of the sponsor include full disclosure to the investigator and ERC of all relevant information regarding the drug, including the results of ongoing trials. Adequate compensation or treatment for subjects who suffer trial related injury or death should also be provided. Important responsibilities of the monitor include facilitation of communication between the sponsor and the investigator, ensuring adherence to the study protocol, and verification of the integrity of data collection. These should be reinforced by regular visits to the investigator before, during and after the trial. The major responsibility of the investigator is the safety of the volunteer. This is maintained by informing the family doctor, by medical supervision of subjects during and after trials, and by provision of adequate resuscitation facilities. Compensation of subjects, after death or injury during a trial, is a major issue which we have dealt with separately (see below).

Compensation for injury

Compensation in the event of injury or death is an area of major concern. It is unreasonable to expect human subjects to take risks for the sake of pharmaceutical development and scientific knowledge, without provision of easily available and appropriate compensation. Many of the procedures have, in the past, been voluntary and, despite assurances, it is possible that a pharmaceutical company or university academic unit might be unwilling or unable to honour its obligations. This would necessitate

Table 3 Investigator responsibilities

1. To be thoroughly familiar with the properties of the investigational medicinal product.
2. To ensure adequate provision of time, subjects, facilities and staff to complete the trial.
3. To provide retrospective data on number of patients who would have been eligible for the trial in order to assure an adequate recruitment rate.
4. To submit an up-to-date curriculum vitae and other credentials to the sponsor and, if necessary, to the appropriate authorities.
5. To sign agreement with the sponsor to work according to the protocol and GCP, to accept monitoring and control procedures, and agree a publication policy.
6. To nominate a local study coordinator, to assist administration, if appropriate.
7. To submit notification/application to relevant bodies, including ERC and hospital authorities, jointly with the sponsor where appropriate.
8. To provide full information to all staff involved with the trial, or the patient's care.
9. To obtain informed consent from subjects before inclusion in the trial.
10. To ensure safe storage and administration of investigation products, and maintain records sufficient for accountability.
11. To manage code procedures and documentation meticulously, in accordance with the protocol, and with the knowledge of the monitor.
12. To collect, record and report data properly.
13. To notify promptly the sponsor (and ERC where appropriate) of all serious adverse events, taking all measures to safeguard trial subjects.
14. To make all data available to the sponsor, monitor and/or relevant authorities for verification/audit/inspection purposes.
15. To certify the data in the CRFs and study reports to be accurate.
16. To sign and forward trial data, results and interpretations to the sponsor.
17. To agree with and sign the final report of the trial.
18. To ensure that the confidentiality of all information about subjects is respected by all persons involved in the trial.
19. To maintain fully functional resuscitation equipment, where appropriate.
20. To ensure appropriate medical care for subjects is maintained during and after the trial.
21. To follow up after the trial all significant abnormal clinical observations or laboratory values.
22. To provide all subjects with a card, including appropriate addresses/telephone numbers, confirming participation in a trial.
23. To mark in the medical records that the subject is participating in a clinical trial.
24. To normally inform the family doctor of trial participation, with subject consent.

(Adapted from the Guidelines on Good Clinical Practice (European Commission, 1990)).

the subject taking lengthy, and possibly unsuccessful, legal action. A case can be made for a legally binding contract with the investigator becoming a legal agent of the pharmaceutical company, and this has been recommended (Association of the British Pharmaceutical Industry, 1989).

Subjects who are involved in non-commercial trials in universities or research institutes do not generally have available the same degree of compensation. It has been suggested that all institutions obtain 'no-fault' insurance to provide compensation for volunteers in clinical trials, independent of proof of negligence or causation (Royal College of Physicians, 1986). However, while reasonably priced insurance may be obtained in some countries, such as Germany, this is not universal. With the opening of the European insurance market in 1992, it is hoped that more reasonably priced cover may become more widely available. Many countries have systems of ex-gratia payments, but these are generally inadequate compared with those in sponsored studies.

In some countries, such as the UK and France, patient volunteers are less likely to receive compensation for injury or illness during a study because the pharmaceutical companies adopt different procedures from those applicable to healthy volunteers (Tunkel, 1989). In France, a distinction is made between research with and without direct benefit to the subject (Ministry of Health-France, 1990). Only in the latter is compensation paid irrespective of negligence or proof of causation; this is defined as 'no-fault' in the French law. Others, such as the Association of the British Pharmaceutical Industry (ABPI), define 'no-fault' differently. The ABPI suggests a form of 'no-fault' compensation which is dependent on a 'balance of probabilities' that any injury is attributable to the medicine under trial, and payable only in the absence of third party negligence, e.g. by an investigator who is not a legal agent of a company (Association of the British Pharmaceutical Industry, 1991). The draft UK guidelines on ERCs state that all commercially sponsored trials (patients and healthy volunteers) should include 'no-fault' compensation for illness during the trial, a solution also recommended by a Working Party of the Royal College of Physicians (Royal College of Physicians, 1991), who highlight the relatively low administrative cost and the benefits of prompt compensation of victims of medical intervention.

The EC GCP guidelines cover few of these issues. They propose that a volunteer should be informed of the arrangements for compensation before consent, and state that compensation or treatment of subjects suffering from drug related injury or death is a responsibility of the sponsor. However, they do not recommend 'no fault' compensation or legally binding contracts between sponsor, investigator and subject, and are ambiguous concerning the responsibility of a sponsor to pay compensation as opposed to providing treatment alone.

Data handling, statistics, and quality assurance

The GCP guidelines on data handling and quality assurance are intended as a system to ensure that only safely and accurately obtained data are used to support applications for drug licences. They cover in detail the verification and archiving of data, the use of statistics (both in trial design and analysis), and the importance of quality assurance throughout the process. Although these aspects are usually of more interest to the pharmaceutical industry than others, they are central to all research. There has recently been increasing public and professional concern about scientific fraud, and rigorous

use of guidelines on data handling and quality assurance may help prevent this problem. Such a system has, in the United States, detected serious deficiencies in the work of 11.5% of investigators audited by the Food and Drug Administration (FDA) (Shapiro & Charrow, 1985).

Discussion

Many reports and guidelines on the ethics of human experimentation have been published over the past decade, although inconsistencies exist. With progress towards an open market in Europe there is a need for a unified approach. In this respect, the EC guidelines should be welcomed as they represent an improvement over the present arrangements. They are, in many respects, similar to the FDA regulations, so simplifying the process of drug licence applications. The degree to which these guidelines will be followed depends both on the willingness of the pharmaceutical industry to submit applications under the centralised EC Committee for Proprietary Medicinal Products system, and on their acceptance by academic researchers. However, due to perhaps deliberate vagueness during the drafting process, or lobbying by interested parties, some sections of the guidelines are inadequate. These are discussed below.

The section concerning ERC membership is vague. This is regrettable and, in view of the new national guidelines for the UK and France, may lead to differences in composition of ERCs between EC countries. In view of the recommendation that ERCs should be capable of ensuring that study design and subject numbers are sufficient to test the hypotheses defined within submitted protocols, the inclusion of members with a clinical pharmacology and/or statistical background should be considered in future guidelines. Presently, it is not proposed that routine examination of studies by ERCs be extended beyond the initial approval of protocols. However, review of interim reports, where appropriate, and of final reports of research might also be monitored by ERCs, as scientific research can only be justified if results are disseminated and published. This would have implications for workload, and members might then need to be remunerated for this largely voluntary work, through handling charges similar to those proposed by the Department of Health in the UK (Department of Health-UK, 1991). It is unfortunate that signed consent is not recommended more strongly. Although written consent does not guarantee that a subject has been adequately informed, and in some circumstances may be inappropriate, at the very least it leaves little doubt in the mind of volunteers that they are entering a research study.

While it is accepted that not all countries within the EC have the same concept of family doctor as that in the UK, the term is used frequently in the GCP guidelines. On this basis, it appears to be a serious weakness of the guidelines that the volunteer's family doctor need not always be informed of participation in a trial, and that a request for past medical history has not been recommended. There is always the risk that healthy volunteers may mislead the investigator about previous illnesses for financial reasons, and there have been serious consequences when this has occurred in the past (Darragh

et al., 1985). There is also no mention of a minimum interval between studies for individual volunteers, who might receive excessive exposure to new drugs or radioactive agents, and lose significant amounts of blood, during over-frequent participation in trials (Vere, 1991). These problems could be avoided by recommending that the family doctor is always sent all information regarding a trial, including any exclusion criteria. In addition, subjects should not be allowed to enter a trial until a positive reply has been received. This should include, and take into account, the length of time a volunteer has been under the care of the family doctor. Alternatively, or as an additional safeguard, and with appropriate protection of confidentiality, the provision of national or a central EC register of research subjects might be considered. These issues should be addressed in future guidelines.

The current EC GCP guidelines do not adequately address the problems of compensation for subjects injured in trials. The guidelines, as written, may allow treatment of illness to replace payment of adequate compensation. In addition, they state that compensation should only be paid in circumstances of 'drug-related' injury, and it is therefore possible that the relationship of a drug to an adverse event may be disputed. In addition, compensation need not be paid if there is investigator malpractice or negligence. Many of these problems could be resolved by recommending that all organisations accept that unexpected injury or illness at the time of, or following a trial should be compensated, independent of causation and proof of negligence, giving the benefit of doubt to the volunteer in marginal cases. This is the view taken by the Royal College of Physicians (1986). Compensation should also be paid by the sponsor in the event of investigator negligence, with subsequent recovery of any payment from this party. This process is not only morally justifiable, but should also reduce time to payment of compensation, and may lower total costs by cutting legal bills.

There are other issues which the EC document has, perhaps wisely, not addressed. Efforts have been made to impose a statutory code of ethics in several countries and the French now have statutory ERCs. Non-statutory guidelines provide more flexibility than a legal framework, although they will only survive if there is adherence to prevailing guidelines. Although the European Commission was open to consideration of comments and suggestions during the drafting of the guidelines, this might not be the case if the European parliament chose to draft statutory guidelines. This body has already attempted to intervene in biomedical ethics by proposing a legally binding charter on patient rights (Laurence, 1989). However, the EC as a whole has no rights by treaty in the health field, and at present initiatives in this area must be unanimously approved by member states.

In summary, we believe the EC has produced a valuable series of guidelines for Good Clinical Practice. It is hoped that the unresolved issues in areas such as ERCs, volunteer registers, signed consent, family doctor involvement and compensation, will be addressed in the next review due in 1992. To encourage wide use of the guidelines the EC should promote their distribution, and ensure they are drafted in a form accessible to practising clinical researchers. If the guidelines are adhered to by both the

pharmaceutical industry and academic researchers, then Europe will have achieved a comprehensive multinational system for protecting the rights and health of human

subjects who participate in medical research. If not, legislation to control human experimentation may be the consequence.

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