Opinion on the testing of new treatments on humans. Considerations and proposals

N°2 - October 9, 1984

Contents

Opinion

Asked by the Secretary of State for Health with the Ministry of Social Affairs for an opinion on the ethical issues raised by drugs trials on humans, the National Consultative Ethics Committee for Health and Life Sciences extended its deliberations to cover all procedures aimed at cure, prevention, and diagnosis in humans (1).

Having considered :

- the need to ensure advances in therapy by an assessment of new treatments and the fact that the so-called controlled trial method is currently the most precise;

- the ethical issues raised by this methodology, especially at two levels, namely :

- the inclusion of a patient undergoing treatment in a group treated according to a pre-determined protocol which in its comparison phase includes the assignment of patients into one of two groups made up so as to be as comparable as possible; and,

- the possibility that trials might be performed on healthy volunteers in the stages prior to the comparison phase; and,

- the national and international rules and recommendations on experiments on humans.

The National Consultative Ethics Committee for Health and Life Sciences recommends :

1) that all trials on humans aimed at assessing a treatment comply with the principles set forth hereafter;

2) that ethical review committees be set up and that all trials be submitted to those committees; the role of such committees would be not only to give an opinion, but also to

compare the views of people from different spheres, and particularly trials specialists and legal experts, so as to gradually generate broad rules;

3) that any applicable legislation be predicated on these principles and the experience cquired through the operation of the ethical review committees.

Principles

- **The duty to test**

It is unethical to administer any treatment which is not known to be the best available or even whether it is effective and innocuous whereas such knowledge could be obtained. Evaluation of new treatments is a duty and must be accomplished in accordance with a strict method, especially:

1) The treatment must involve a comparison phase, using a control group receiving a reference treatment (or no treatment if none is acknowledged to work); in the comparison:

- treated groups and control groups must be constituted in such a way as to make them as comparable as possible; the only rigorous method in the current status of knowledge is randomisation, which entails drawing patients by lot;

- in some cases, the name of the treatment must remain unknown to the patient and even the doctor, with the treatment for testing presented in a form which is indistinguishable from that of the reference treatment. If such is the case, and there is no recognised active treatment, the reference treatment is a placebo.

2) Treatments, and especially drugs, must be tested on humans prior to the comparative phase with a view to elucidating the mode of action and the level of tolerance. Most of such trials must not be performed on patients suffering from an illness: they require the co-operation of healthy volunteers. Accordingly, trials on healthy volunteers are indispensable. However, in France they are held as illegal. The situation calls for the intervention of the lawmakers.

- **Conditions**

The trials described above are acceptable only if a number of conditions are strictly observed. Five are imperative: adequate "pre-requisites", the scientific value of the project, an acceptable risk-benefit balance, the patient's free and informed consent, and the scrutiny of the trial by an independent committee.

1) " pre-requisites" obligation

No trial procedure can be performed on human beings unless all the guarantees which can be provided by laboratory in vitro pharmacological and toxicological experiments on a large enough number of subjects from several animal species are given.

2) The scientific value of the project

A trial run on insufficient scientific bases in comparison with the current status of knowledge is unethical: Firstly, it makes needless demands on patients and more importantly, it might lead to faulty conclusions which will harm future patients. Hence, a trial may only be undertaken by a qualified team comprised not only of clinicians, but also at least one specialist in the methods of controlled trials (for the comparison phase) or in pharmacology (for the phases prior to comparison).

3) An acceptable risk-benefit balance

This audit must be approached differently for patients included in the study while they are under treatment, in comparison with healthy volunteers.

a) *Patients included in trials during treatment (sufferers or subjects at risk undergoing preventive treatment).*

Two objectives must be met simultaneously and under the best possible conditions, namely: to treat the patient and to assess the treatment. Reconciling these two requirements can be problematic, especially in the comparison phase. In this regard, a distinction must be made between two possibilities :

- because of its expected (though unproved) benefits and its harmlessness (albeit not totally established) the new treatment can in all good faith be considered equivalent to the reference treatment. This the " equal value" situation. Placing a patient in either group, however the groups have been made up, poses no problems in terms of his/her well-being. Then the optimum solution is the one which makes the trial valid by constituting comparable groups using the rigorous methods already mentioned, especially randomisation; and,

- the two treatments are not deemed equivalent. In most such cases, the trial generally cannot be contemplated. However, a review must still be made taking into account the well-being of the patient, which must be the top priority, but also the interest of society as a whole, which cannot be completely disregarded: if the expected benefit for the community is very great and the drawbacks for the patient only minor, the trial could be considered by way of an exception. For instance, a trial in which the control group is to be given no treatment or simply a placebo when there is a treatment known to be active on the disease cannot be contemplated as a general rule. Yet it could be, as an exception, if it entailed only a minor and temporary disorder and were to test a new class of molecule.

When a new treatment emerges, the " equal value" situation is the rule; this is why any new treatment, in principle, can be subjected to a comparative trial.

b) Trials on Healthy Volunteers

Unlike the situation described above, in this case the subject can expect no improvement. The trial is acceptable only if, on balance, the risk encountered is minimal. Inter alia, this requires adequate infrastructure to ensure the subject's safety.

4) Free and informed consent

This must also be considered differently depending on whether we are dealing with patients included in a trial while undergoing treatment or healthy volunteers.

a) *Patients included in a trial while undergoing treatment* . Consent must be on two counts: to the treatment, and to the trial.

Consent to the treatment must be elicited in accordance with the rules normally observed which mention free and informed consent. Any limitation on information given to a patient is acceptable only insofar as this is in the patient's interest and the physician does not breech the patient's trust.

Except otherwise justified, free and informed *consent to the trial* must be sought in the interest of the patient :

- informed consent

In many cases, the patient can, and so must, be given full information about the aim,

protocol, and performance of the trial; however, in some instances it could be acceptable to provide limited information in the interest of the patient. Both consent and information can be given verbally or in writing. A general rule cannot be established; but the way in which the consent is to be obtained must be stipulated when the protocol is presented to the ethical review committee.

- free consent

The patient must be fully able to agree or refuse to enter the trial and to leave it at any time without explanation. No coercion, however slight, exerted in this connection can be tolerated.

If trials are to involve legally incompetent subjects, consent must be obtained from those who hold parental authority over unemancipated minors or the legal guardians of minors under tutelage and of legally incompetent adults protected by court order. The consent of a legally incompetent person also may be required whenever he/she is deemed capable of expressing his/her wishes.

b) *In trials on healthy volunteers* , consent must be fully informed, with the subject informed about the aim, protocol, and performance of the trial, and entirely free. Consequently, it is unethical to conduct such trials on prisoners, on the mentally incompetent, and on patients suffering from a disease unconnected to the study. People in the last category are sometimes taken as healthy subjects whereas they are in a relationship of dependence with the attending physician; hence, the likelihood of such situations occurring must be precluded.

If the trials are to be conducted on people dependent on the instigator or of the person in charge of the scientific inquiry, or on medical students, this fact must be mentioned in the protocol submitted to the ethical review committee.

Consent is a " trial contract" . It must be subject to a written agreement signed by both parties. The agreement must describe the obligations of each party; furthermore, it must stipulate the amount payable to the volunteer. This can be nothing more than compensation for the inconvenience suffered. Under no circumstances can any financial reward be paid. Thus, the amount payable can not be taken as incentive for volunteers to participate. Volunteers must not take part in trials too often. To cover any injury attributable to the trial, its initiator must take out insurance.

5) Examination by an ethical review committee

Whether in the comparison phase or the stages leading up to it, the trial must be examined by an ethical review committee. The committee must ensure that the four obligations set out above have been met properly and in the order stipulated herein. If one condition is not met, no further examination of the subsequent conditions is required. The assessment is expressed as an opinion and does not relieve the investigator of responsibility. If the trials are to be performed on healthy volunteers, a favourable opinion of the committee is absolutely necessary.

Hereafter, proposals are presented for the establishment and operation of the ethical review committees.

Role of trials in the advancement of therapy

For certain diseases, it would be useful to set up a structure to examine the contribution of trials. That structure would be based on a recording of the trials from their beginning. Another advantage of having a structure such as this is that it would publish negative outcomes, which often go undisclosed.

As yet, trials have not been given their rightful place in the furthering of therapy. The keys

to much-needed improvement are training (of trails specialists and physicians who use trials) and information (rapid dissemination of results).

Proposals for the creation and operation of ethics committees

The National Consultative Ethics Committee for Health and Life Sciences recommends the creation of ethical review committees, the membership and operation of which should be determined by regulation. It further recommends that all trials on humans be submitted to such a committee for it to assess the benefits of any curative, preventive, or diagnostic intervention.

The decisions of the ethical review committee assessing a trial must be unequivocal so as to rule out any choice and to prevent a request being made to several committees simultaneously. The best solution would appear to be to partition the country into zones each with one committee. The " instigator" of a trial would have to apply to the committee of his/her zone. A " zone" could be an administrative area, a group of administrative areas (if the volume of work is small), or a subdivision of an administrative area. The advantage of this arrangement is that it would ensure committee rulings were unequivocal. Even for a multicentric study, there would be no alternative: there is always one initiator or instigator, and the relevant committee would that of his/her zone. Committees should be set up gradually and take into account the accomplishments of certain ethical review committees already in existence.

Co-ordination must be instituted between the committees at all levels. It could be carried out by the national committee. The membership and creation of the committees should be determined by an official document which sets certain rules but leaves room for ample flexibility in their application. The National Consultative Ethics Committee for Health and Life Sciences can make a number of proposals in this respect.

A committee must issue its opinion within a short time as trials can not be held up by bureaucracy. If the committee fails to reply in due time, the application could be referred to the national committee. Opinions handed down by regional committees can be contested by application to the national committee.

The role of the committees should not be restricted to the analysis of trials focusing on prevention, cure, and diagnosis: they should also examine all the moral and ethical issues raised by research into biology, medicine, and health.

The committees will have a heavy work load. They must be given the required personnel and finance.

Ethical issues raised by the testing of new treatments on humans. Considerations and proposals

Preamble

Experimentation on humans is performed in many and varied circumstances, from the first *in vitro* fertilisation through the examination of the effects caused by an additive to a food product to purely scientific tests designed to further knowledge. This document deals only with curative, preventive, and diagnostic trials plus experiments intended to analyse the

trials using the suitable methodology. This is a precise topic; but it is quite broad nonetheless and of concern to many. This methodology involves two measures which cause major problems: the first is the arranged inclusion of the patient in a group for treatment according to a pre-determined protocol; the second is experimentation on healthy volunteers. Hence, particularly if they are hospitalised, patients wonder whether they might not become experimental objects; researchers ponder the legality and the ethics of their work; and, if litigation occurs, magistrates encounter a problem for which they are unprepared. The aim of this document firstly is to give information - hitherto lacking, and sometimes seriously - to all concerned both on the methodology of such experiments and the ethical questions raised; and secondly to set out some proposals.

Medical evaluation was first applied to *curative* procedures. For a long time this was done empirically on the basis of impressions and approximations. Approximations might suffice for treatments indispensable from the outset such as streptomycin to manage the previously fatal tuberculous meningitis. However such successes are few and far between and therapy mostly progresses through a succession of modest advances which can only be confirmed and made clear by rigorous analysis. Only since the fifties has a truly scientific methodology been developed, based primarily on a statistical approach. Later on, with the development of effective preventive measures, evaluation was extended to preventive medicine; and subsequently it was contemplated for the comparison of diagnostic procedures. In both these areas, the methods of reference have been those applied to curative treatmentsand so they will be the first described.

" Treatment" refers not only to drugs, but also surgical procedures, radiology, implants, and so on.

After they have undergone the required laboratory tests in vitro and on animals, drugs are tested on humans in a process which can be divided roughly into four stages as follows:

Stage 1 is the tolerance study.

Stage 2 is designed to give preliminary information on efficacy, how the drug is metabolised, and the best means of administration. Stages 1 and 2 involve a small number of subjects (fewer than ten, to a few dozen at most), either suffering from an illness or healthy volunteers.

Stage 3 aims at methodically assessing the new treatment and placing it within the arsenal of existing therapies. It can involve from a few dozen to - as is most often the case - several hundred patients and can last from a few months to (more frequently) a few years. It must be conducted according to a very elaborate method.

Stage 4 is more recent. It entails monitoring the drug once it has been marketed, the main objective being to detect any unwanted side effects which might be uncommon and/or of late onset and not revealed during stage 3. The length of stage 3 and the number of subjects in it are necessarily limited. Stage 4 involves a very large number of subjects (easily several thousand) and is based essentially on observation by physicians for undesirable side effects.

Testing of non-drug therapy (radiotherapy, surgery, etc.) is more difficult to divide up into four stages. In all cases however, stage 3 remains the crucial phase in assessing a treatment. Very rigorous - by virtue of the contribution made by statistical methods and the gradual enhancements made over 40 years of implementation - " controlled therapeutic trials" are a whole subject in their own right.

In such trials, the group receiving the new treatment is compared to a control group which is receiving standard treatment - considered the best available - or no treatment if there is no recognised active therapy. Comparison can centre on aspects other than efficacy (especially tolerance). The control group is indispensable. For instance, it is not possible to assess a treatment for infertility by the number of pregnancies achieved in a treated group

as the subjects are not totally infertile but rather hypofertile and the same number of pregnancies could have been achieved in the same period of time had no treatment been applied. In short, *evaluation implies comparison.*

The comparison of groups is not merely an examination of percentages (cure rate, death rate, etc.) and averages (mean term of the disease and so on), for such statistics can only be determined to within a certain margin of error depending on the size of the group. Comparison requires a suitable *statistical test* : a test based on the calculation of probabilities can tell whether the difference observed is significant or due to sampling fluctuations.

A significant difference found between the groups is not necessarily due to the treatments applied. Such a conclusion can only be reached if the groups are strictly comparable in all respects other than the treatment. It is very difficult to make up comparable groups. Groups of patients cannot be considered comparable if over a given period they " happen to" have received one of the treatments being compared; for instance cancer patients treated with radiotherapy and those treated with surgery, quite simply because the cancerologist will refer the cases with the best prospects for surgery. Neither can cases from two different periods be considered comparable, although this is less clear-cut. By way of an illustration, in a large Paris hospital the death rate for a given type of cancer had grown steadily from year to year. The explanation was that the arrival of a renowned senior residentattracted more and more serious cases. The mere launching of a trial can modify candidate intake; thus when it was suggested that anticoagulants could prevent a recurrence of infarction, a test was planned in the United Kingdom. The project became known to the public and drew a larger-than-average number of less serious cases. The shared flaw running through these examples is that the groups for comparison emerge spontaneously depending on the characteristics of their members or a particular development - which renders them incomparable. The difficulty is the same as that encountered in opinion polling when pollsters seek to determine a " representative" sample; that is, one which is comparable to the rest of the population from which it is drawn. It is acknowledged that the only precise way of obtaining comparable groups using the current knowledge available, is to divide subjects into two groups by randomisation, in which subjects are drawn indiscriminately.

However, comparable groups at the start of the trials might lose that comparability as the trial progresses simply because subjects become aware of the treatment received. Firstly in terms of judgment criteria, the person making the judgment might be biased - albeit subconsciously - and favour the treatment she/he thinks the best. More importantly, the course of the disease can be affected by suggestion. Firstly, auto-suggestion can be involved. Studies have shown that a placebo (inactive pseudo-treatment identical in its appearance to the active treatment) in many cases can induce the benefits of the real treatment, and sometimes even its side effects. It has also been observed that hetero-suggestion can be at work: hetero-suggestion can influence the course of the disease. To prevent such bias, tests have been designed which ensure that subjects or both doctors and subjects are unaware of the treatment administered. This is the *double-blind or double-unknown* trial in which the treatments to be compared are presented indistinguishably so that neither doctor nor subject know what the treatment is. The treatments can be the treatment tested and a placebo which looks the same as it. It is not always possible - or indeed necessary - to take such precautions, but if they are not practised this must be considered when critically interpreting the results.

The requirements of a control group, a statistical test, randomisation, and sometimes " working blind" are essential to stage 3 of the trial and are known and accepted by an ever increasing number of biologists and doctors. However, at each step - in formulating the problem, in setting the protocol, in conducting the tests, and in analysing the results - all trials raise difficulties as revealed little by little over the past decades and which have been solved through a methodologically determined approach. Some such difficulties have been chosen as examples and are described in appendix 1. They are veritable " pitfalls" which are avoidable, but only by someone specialised in this field. If they are not avoided, there could

be two serious outcomes: the conclusions of the trials will be unusable or - worse still - they will be faulty.

The evaluation of *preventive and diagnostic* procedures quite logically should be performed in accordance with the same principles - as it sometimes is. However, the methods of controlled therapeutic trials can prove extremely difficult to implement in trials on preventive medicine. This is especially true of the formation of groups as it is sometimes impossible to isolate individuals. Such is the case when the trial is to test the effects of a food additive, or the impact of a publicity campaign to modify behaviour. One solution is to take not individuals but communities as the basic units. Thus, in a multifactorial prevention trial on cardio-vascular disease in France involving the employees of a major public service, it was not possible to prescribe different diets to the staff members of the same department; hence, two groups of departments were randomly constituted and each was prescribed one of the two diets examined.

The complex machinery of these trials might appear unrealistic and its usefulness doubtful.

Unrealistic? From 1970 to 1980 nearly 1,000 randomised trials were recorded world-wide on cancer alone.

Useless? One example will be given: in 1957 the Salk poliomyelitis vaccine passed the laboratory tests which proved its effectiveness and harmlessness in animals. Its protective power still had to be tested on humans. A trial was run in the U.S.A. on nearly 400,000 children half of whom were chosen by randomisation and were given a placebo. Thus, proof of the vaccine's efficacy was obtained in fifteen months, thereby enabling its widespread use very quickly. These results are particularly striking when we remember the interminable controversy over the BCG vaccine which had not been tested in this way from the start.

Clearly indispensable and widely practised, scientific assessment of the effects of a treatment can seem disturbing nonetheless, especially in stage 3. Randomisation and " working blind" , to mention but the most conspicuous aspects, are problematic: have we not moved from designing therapies for the treatment of patients to using patients to assess therapies? If both approaches are used simultaneously, is the well-being of the patient safeguarded? These trials must be put into their national and international ethical, regulatory, and legal context.

The essential ethical principles have been set down, particularly in three international instruments: the Nuremberg Code (1947), the Helsinki Declaration (1964) revised in Tokyo (1975) of the World Medical Association, and the guidelines proposed in Manila (1981) by the World Health Organisation and the Council for International Organisations of Medical Science.

The Nuremberg Code includes ten articles which stipulate the conditions under which experimentation on humans is allowable. Given the place and time it was promulgated, it is understandable that the code should contain the requirement of voluntary consent as its first article.

The more detailed Helsinki-Tokyo Declaration introduced the obligation to submit the protocol to an independent committee appointed specifically for that purpose. The consent of the subject must be free and informed, and preferably in writing. If the subjects are suffering from a disease such that the doctor considers they must not be asked for informed consent, he/she must give an explanation in the protocol submitted to the independent committee. The Declaration clearly makes provision, under certain conditions, for " purely scientific" experiments of no therapeutic benefit to the subject (the subject being a healthy volunteer or a patient suffering from a disease unrelated to the test).

The Manila Declaration specifies the ways in which the Helsinki-Tokyo Declarations are to be applied, especially in developing countries. It emphasises that informed consent is an inadequate safeguard and that it must be completed by an examination of the ethical issues

by an independent committee. Furthermore, it is accepted that it is impossible to obtain informed consent in many cases: not only from the legally incompetent such as children and the mentally ill, but also from people unaware of modern medical concepts. In such circumstances, the examination by an independent committee is imperative.

The independent committees, termed ethical review committees, should not only focus on ethical issues. Indeed, it is stipulated that no boundary line can be drawn between ethical assessment and scientific assessment since any experimentation of no scientific value would be unethical ipso facto. Therefore, ethical review committees should examine scientific aspects as well.

These declarations are intended to " guide the world's physicians" . They are given in full in appendix 4.

Prior to 1941, the sale of pharmaceuticals was not subject to any legal requirements " in France" . In that year, it was made compulsory to obtain ministerial certification. This rule was replaced by another regulation termed " the marketing-authorisationstatute" (autorisation de mise sur le marché). It was the outcome of a decree dated 23 September, 1967 from the code of public health and completed by edicts on its application in 1972 and 1975. The latter state that the assessment of a medicinal requires comparison with a control group in observance of a strict protocol based on the statistical method, with the trial run using the " double-blind" technique. Such trials are to be made known to the Direction de la pharmacie et du médicament. Thus, not only is the stage 3 trial allowed - it is compulsory in order to secure the authorisation to market a drug. Non-drug treatments are not subject to any regulations.

Trial therapy of a patient has two legal aspects. Firstly, the doctor-patient relationship as it exists in everyday practice (quite apart from any testing) is considered as a contract; hence, it is subject to the general obligations of any contract, including free and informed consent, as defined by the code of civil law and case law. Secondly, since trials on humans are involved, the New York International Pact on Civil Rights, to which France acceded in 1976 and of which article 7 stipulates that it is forbidden to subject any person to a medical and/or scientific experiment without his/her freely-given consent, makes it mandatory to include an additional clause. Therefore not only does the subject consent to treatment, but also to participation in the trial. The definition of consent - and especially informed consent - is open to debate. A 1961 ruling of the Cour de cassation (France's supreme court) states that the information given to the patient should be simple, approximate, intelligible, and sincere - all of which adjectives leave room for imprecision.

As to healthy volunteers, the experimentation allowed in many countries is neither explicitly authorised nor forbidden in France. However, most jurists consider that the contract between the investigator and the subject is illicit since there is risk without benefit.

Indeed, the opposite case could be put by referring to the New York Pact: that is, if it is forbidden to subject anyone to medical experimentation without her/his consent, then if such consent is obtained the experiment is lawful; and the article does mention a subject rather than a patient. However, international law does not overrule national legislation when the latter is more protective of the subject - as is precisely the case in contract law in France as interpreted herein. Hence, this type of experimentation appears to be illegal in France.

As well as the most significant instruments already mentioned, there are a number of others both national and international dealing with ethics, regulations, and legislation. The Conseil de l'ordre des médecins (the governing body of France's medical association) has taken a stance in a comment to the medical code of ethics. More instruments are needed. Documents are not always consistent with each other; furthermore, they must be made to accommodate widely differing cultures and so be geared to each country. At present, the French public consider it is sufficiently protected. The same applies to those who carry out trials (researchers, clinicians, and the heads of the pharmaceuticals industry).

Legislation to correct the situation regarding medication trials is being prepared. The committee in its entirety is of the opinion that such trials must be submitted to an official ethical review committee. Such committees would comprise eminent persons from various fields and particularly jurists and people working with medical trials. Not only would they scrutinise the ethics of the trials, but also compare views on the problems raised. Gradually, this would enable general rules to be developed. Some of the legislation now being examined could be expanded upon at a later date depending on the experience gained in the meantime. In addition, a number of principles drawn from the various international declarations should be set forth and adapted to our country. They would be made known to the ethical review committees, magistrates, and the public. Ample information is indispensable if opinions and behaviours are to develop rationally.

This is the spirit in which the committee is proposing both a number of principles and a modus operandi for the ethical review committees.

This document deals not only with drugs testing but also with all experimentation on humans of any surgical, radiological, or other procedures performed for cure, prevention, or diagnosis.

Principles

The principles which follow concern the ethics of experimentation on humans when it is performed to assess any medical, surgical, radiological, or other procedures performed for cure, prevention, or diagnosis.

Principles

The principles which follow concern the ethics of experimentation on humans when it is performed to assess any medical, surgical, radiological, or other procedures performed for cure, prevention, or diagnosis.

Because each human is unique, any act, whether unprecedented or tried and tested, performed on a human is an experiment of sorts; however, it shall not be considered as such under the principles set forth herein unless it involves a study covering several individuals in compliance with a pre-established protocol and is designed to give a broadly applicable outcome.

From the outset, two classes of experiments must be distinguished. The first concerns patients included in a trial as part of their treatment and the second involves healthy subjects - inevitably volunteers - included for example in stage 1 of a tolerance trial. These two types are commonly referred to as " experiments on patients" and " experiments on healthy volunteers" . However, patients included in trials as part of their treatment might well be healthy, if the trials are on preventive medicine. Hence the term " trials on patients or subjects at risk" appears more appropriate. One important difference between the two situations is that in the former the subject can expect to derive some curative, preventive, or diagnostic benefit from the trial whereas this does not apply in the latter situation. " Experimentation on healthy volunteers" should be known as *trials with no personal benefit* . In the first instance, a personal benefit can be expected - though it is not certain: when a new treatment is compared to a conventional therapy, the patient would have been put on the established treatment had he/she not been included in the trial. Inclusion in the trial can be of benefit only if the patient is placed in the group receiving the new treatment and that treatment is the better. These are *trials with potential personal benefit* .

Each of these situations will be considered separately.

A) Trials on patients or subjets at risks as part of their treatment (trials with potential personal benefit)

These subjects, whether patients or individuals at risk (preventive trials), will be termed patients. For convenience, the procedures to be tested - including diagnostic procedures - will be termed treatments.

Treatments applied to patients in the course of their therapy have been assessed for as long as there have been medical practitioners providing care and observing the results. Such assessment must conform to an appropriate methodology, typical of experimentation, and of which the outline was given in the preamble.

Since there is now a strict method available, investigators are duty-bound to use it whenever possible. It is unethical to administer treatment which is not known to be the best - or even effective - whereas such information could be obtained. There is a " duty to test" ; not only medication, but also surgical, radiological, and other treatments. New treatments should be tested as early as possible for if there is too great a delay they may become widespread and be taken, without proof, as " the best" available. Then no longer will it be possible to provide such evidence as it will be considered unethical to form a control group excluded from the treatment.

Hence, the physician faces two ethical requirements as follows:

- in the interest of the patient, he/she must administer what current medical science considers to be the best treatment; and,

- the well-being of the community demands that the treatment administered contribute to an improvement of therapy.

Both necessities are closely linked: doctors treat their patients as best they can with the benefit of findings on earlier patients; and they will treat tomorrow's patients better if today's patients are included in trials.

However, both approaches do not go always hand in hand: doing the best by the individual does not mean necessarily doing the best for the largest number and vice versa. Hence, the convergence and divergence of the two imperatives need to be examined.

When a new treatment is proposed for a comparative trial, it is assumed - on the basis of theoretical considerations, laboratory tests, and stages 1 and 2 of the experimentation on humans - to be superior to conventional treatments. However, definitive proof of its superiority has not been provided as no comparative trials have been run and the new treatment is perhaps inferior. Furthermore, some aspects of the treatment are still unknown. These disadvantages can outweigh the expected benefit. Practically speaking, most trials involve some additional restrictions but these are counterbalanced by more frequent, and therefore better, monitoring. On balance, both treatments sincerely can be considered equal: the old and the new therapy can both be considered the best available. This is the " equivalent treatment" situation. In this case, there is no problem placing the patients in one group or the other from the point of view of the patient's health, no matter how the groups have been formed (hospital X versus hospital Y, period X versus period Y, randomisation, etc.). The optimum solution is the one which makes the trial valid, with the formation of two groups as comparable as possible using the methods described in the preamble, especially randomisation. Thus, the well-being of the individual can be reconciled with that of the wider community. The " equivalent treatment or " equal value" situation should be the rule if the trial is undertaken soon enough after the emergence of a new treatment. The time factor is important, for too long a delay could cause " impressions" to be formed which though unfounded do complicate the situation.

However, in some cases the benefit of the individual does not coincide with that of society at large. For instance, for the efficacy of a new molecule to be tested, a proper trial would

require comparison with a non-treated group, or even a group which had received a placebo. However, for the disease studied, there are treatments proven to be active by tests in which the proper methodology was used. Inclusion of the patient in a such a trial is clearly against his/her best interests.

These considerations show that the decision to undertake a comparative study raises two questions. If the trial involves " equivalent treatment" , it is acceptable; but are both treatments truly equivalent? This is the first question. If the treatments are not " equivalent" , and if the benefit to the individual and the well-being of society differ, then clearly the interest of the individual must take precedence. However, the welfare of the wider community, the benefit of tomorrow's patients, cannot be overlooked entirely. Can the trial be run under certain pre-determined conditions? This is the second question.

The preceding considerations illustrate the problems faced when including a patient in a trial as part of her/his treatment. The mere reconciliation of individual and community interests means that certain conditions must be met. Additional conditions must be fulfilled before experimentation on humans can even be contemplated. In all - to mention but the most essential - five basic obligations must be fulfilled: sufficient preliminary studies, trial designed on sound scientific foundation, acceptable risk/benefit outcome, patient's free and informed consent, and appraisal of the trail by an independent ethical review committee.

1) Mandatory " pre-requisites" .

No experimentation can be performed on humans unless all the guarantees provided by pharmacological and toxicological tests done in the laboratory, in vitro, and on large enough numbers of several animal species are provided.

2) The scientific soundness of the intended trial.

It cannot be stressed enough that a trial undertaken on flawed scientific grounds (compared to current knowledge) is unethical. Firstly, it makes needless demands on patients; but more importantly, it can lead to erroneous conclusions detrimental to future patients. Therefore, trials must be meticulously prepared, conducted, and analysed, which due to the many possible mistakes referred to in the preamble, requires a skilled team comprising not only clinicians but also at least one controlled-trial specialist.

3) Adequate risk/benefit balance.

No experiments can be done unless the risk/benefit outcome is adequate; that is the balance between the risk taken by the patient weighed against the benefits for the patient and the community. This audit must take several factors into consideration: frequency and gravity of the disease, efficacy and risks of treatment, and many more. In all likelihood, some of these parameters are not known with accuracy, precisely because the trial has not been performed. Nonetheless, they can and must be estimated.

It is essential to ascertain whether a trial is to involve " equivalent treatments" and if not, to determine whether any exceptional circumstances would enable the trial to go ahead regardless. In the example given above (the assessment of the efficacy of a new molecule versus an untreated group or a group receiving a placebo) the treatments cannot be considered as " equivalent" if there is a recognised active therapy for the disease concerned. Therefore, such trials are generally deemed unethical. However, if the inconvenience and/or discomfort are slight and the prospect of a useful therapy being discovered substantial, the trial could be contemplated exceptionally.

4) Free and informed consent.

International declarations and national stances, in addition to national and international law (France's accessionto the New York Pact) unequivocally specify that the patient's free and informed consent is a pre-requisite. However, this point is unclear as regards both its

definition and its solution (not to mention the condition of the legally incompetent, which will be discussed further on). A clear distinction must be drawn - as is mostly not done - between consent to treatment and consent to the trial.

a) *Consent to treatment* goes beyond the area of trials: it has to do with any curative, preventive (or diagnostic) measure currently practised. Systematic consent after the patient has been fully informed, as is the case in the United States, poses problems - if only because of the distress caused to patients by the disclosure of a sometimes fatal disease and an interminable list of possible side effects of the treatment which might or might not occur. It is not the custom to ask explicitly for consent in France, except in special-risk cases. Doubtless, consent is not sought as much as it should be; nonetheless, the principle is rational - though not so easy to implement. Free consent, which goes without saying, is generally limited by the authority of the doctor. Informed consent is more problematic. Firstly, even the doctor often is unsure; but more significantly it is considered acceptable in our culture to hide from a patient the diagnosis and/or risks of serious although unlikely outcomes. The borderline between what must be and what can be told to the patient basically is determined by two principles. Limits on information are acceptable if: a) it is in the interest of the patient; and, b) the doctor does not breech the patient's trust.

Patient inclusion in a trial would not create a situation any different to that in practice were it merely a matter of monitoring the case as part of a series of observations. However, the allocation of patients into groups following a pre-determined protocol, and possibly by randomisation, adds a further purpose. Can this be kept from the patient without transgressing the two principles described? Perhaps it can, when both treatments are " equivalent" . Yet it is still questionable. Furthermore, the boundaries of the " equivalent treatment" situation are not always clear. Additional consent is required: consent to the trial.

b) *Free and informed consent to the trial* can take on many aspects. Let us consider information first. In principle, information must be comprehensive: the patient is informed that he/she is being included in a study; he/she is told of the purpose and methods, including the fact that groups will be formed in stage 3 by randomisation; and, the protocol, the requirements on the patient, and double-blind procedure (if applicable), etc. are described. This approach is the most consistent with international declarations (and the law). It is the best. Yet flexibility of application is needed to accommodate the wide variety of situations.

Firstly, there are different pathologies. Diabetics generally have to come to terms with their disease. They tend to know all about the related risks and treatment; hence, they can - and therefore must - be fully informed with a view to their inclusion in a trial. Likewise, in a recent trial of a viral-hepatitis vaccination, the subjects were able to receive full information including reference to a placebo group. However if cancer sufferers are told they are to take part in an experiment, it could serve to increase their anxiety and work against them; so information would need to be metered out, depending on the situation.

Secondly, there is a diversity of cultures. If the French are less inclined than the Americans to give information on diagnosis and treatment, the same must apply to information on participation in trials. Furthermore, some patients are less educated than others and so less able to understand the principle of the trial. They can either be excluded from the trial if they are few in number and if the standard applied is that of full information; or else, the principle of different approaches for different patients might be entertained.

In the final analysis, no one solution seems applicable in all instances given the present habits of patients and the medical community. Only the principle can be stated that the rule should be full information; that incomplete information must be the exception and justified; that in all cases the degree of information must be stipulated in a document appended to the protocol submitted to the ethical review committee; and, that such exceptions should become less and less common once behaviour has been changed by the exercise of free and informed consent.

Thirdly, consent must be free. This means that the patient should be entirely capable of agreeing or refusing to take part in a trial, and to withdraw from it at any time and without explanation. This rule must be applied to the letter.

Consent can be asked for and obtained by the doctor taking part in the trial. The advantage with this is that he/she knows the issues better than anyone else. The drawback is that the doctor might be biased. The presence of another person might be envisaged - a doctor in attendance, a nurse, or an " outside witness" . Information can be given verbally but preferably should be provided in writing in a short, understandable document which sets forth the essentials, that patients can read at home at their leisure, and that they might even show to their family or others. Consent can be given verbally or in writing. Written consent protects the doctor more than it does the patient. Once again, it appears impossible to develop a blanket rule.

c) If trials are to involve the *legally incompetent* , consent must be obtained from those who hold parental authority over unemancipated minors, or from the legal guardians of minors under tutelage and of legally incompetent adults, with the introduction of all the nuances necessary to cover the diversity of categories. This point is further developed in appendix 4.

d) *Trials on large populations* (for instance, on the effects of insecticides or the addition of fluorine to salt, etc.). Consent should be obtained from a body representing of the community concerned.

5) The opinion of an ethical review committee.

The trial - whether stage 1, 2, 3, or 4, must be submitted to an ethical review committee. Essentially, the role of the committee is to ensure that the four obligations already detailed herein have been properly fulfilled, namely that:

a. sufficient preliminary test results are available;

b. the planned trial is scientifically sound. The examination requires the participation on the committee of specialists in trial methodologies. Prior assessment of the trial by a scientific committee might lessen - but not obviate - the involvement of the ethical review committee. The committee must also make sure that the team to perform the trial has the required capacity to do so;

c. the risk/benefit outcome is acceptable; and,

d. the procedure applied to obtain free and informed consent is satisfactory given the conditions specific to the trial.

Verification is performed in the order as given. If any condition is not met, compliance with the subsequent conditions is not examined.

The assessment is given as an opinion (favourable, favourable with reservations, or unfavourable) and not an authorisation. The opinion does not relieve the investigator of responsibility.

Last but not least, another role of the committee, as mentioned in the preamble, is to compare the views of people from different backgrounds and especially doctors, research workers, and jurists, so as progressively to improve a common doctrine on ethics. In this respect, it would be preferable if the people in charge of a trial were invited to those sessions of the committee in which their project is discussed. It would also be advisable for the committees to make their work widely known to the authorities concerned.

If obtaining the opinion of the ethical review committee were discretionary, many

investigators would undoubtedly opt for this approach to cover themselves; however, the most questionable trials might escape scrutiny. Therefore, it must be made mandatory.

Proposals have been made in appendix 3 on the establishment and operation of ethical review committees in keeping with the duties described here.

B) Trials on healthy volunteers (trials with no personal benefit)

These are trials on healthy subjects and are not connected to any treatment prescribed for them. The goal is to acquire knowledge about a treatment - essentially a drug. These insights are sought in stages 1 and 2. They are parameters related to the kinetics and metabolism of the substance, its dose/effect relationship, and especially its harmful side effects.

Such understanding is indispensable. It is not enough to assess the effects of a treatment - for instance by a stage 3 trial - without understanding how it works. Moreover, stage 3 cannot be undertaken without having explored and chosen the ways in which the treatment is to be administered; however, tolerance is of the utmost importance. Everything must be done to ensure the required safety before any substance can become a medication. There now exist for most diseases a number of treatments which are equally effective and new therapies might result only in minimal improvements, the main issue becoming that of tolerance. In another vein of thought, many " alternative medicines" are becoming more widespread. Some of them appear to have no more effect than a placebo; yet we must be certain that they have no harmful side effects. In short, today tolerance is as important as efficacy - and often more so.

Stage 1 and 2 studies are performed by administering gradually increasing doses - single doses to begin with and then if outcomes allow, repeated doses. This is done until signs of intolerance begin to appear. In many cases, such tests on patients are unthinkable for several reasons. Firstly, it is unthinkable to administer to a patient in addition to his/her prescribed treatment, any poorly-known new substance at doses initially ineffective but thereafter increasing to a point where they cause signs of intolerance. Neither is it conceivable to expose a patient to multiple and repeated tests which are of no personal benefit. Furthermore, the results of such investigations could well be uninterpretable due to the characteristic heterogeneity within a group of patients and interference with medication they are already receiving.

Generally speaking therefore, such experimentation can only be carried out on healthy subjects; but it exposes them to risks and constraints with no expected personal benefit. This is why the French authorities presently consider that such trails are unlawful whereas they are allowed and widely practised under certain conditions in other countries.

It seems indispensable for the French authorities to revise their stance and make these trials legal; of course on condition that a number of principles be strictly adhered to. Five obligations must be met - the same five as for trials with potential personal benefit, but some of which will involve different application procedures.

1) " pre-requisites"

obligation. Goes without saying.

2) The scientific value of the project.

In this case it has less to do with the statistical aspects than with the pharmacological considerations. It requires a team of high calibre specialised in clinical pharmacology.

3) An acceptable risk-benefit balance.

The advantage for society is obvious but the subject faces risks and constraints without any expectation of personal benefit. This situation is entirely different from that of patients included in trials while undergoing therapy. Trials on healthy volunteers should entail minimum risks. Inter alia, this requires infrastructure reliable enough to guarantee the safety of the volunteer.

4) Free and informed consent.

It must be obtained under extremely strict conditions.

It must *fully informed* . The information not only on the treatment but also on the participation in the experiment must be complete and detailed. It *must be entirely free* ; hence trials of this type are unethical if they are to involveprisoners or legally incompetent subjects. In some circumstances, particularly under the Tokyo-Helsinki Declarations, trials with no personal benefit can be performed on sufferers of a disease unrelated to the study - who for this purpose are taken as healthy subjects. Obviously, the boundary between health and sickness is not absolute and sufferers of minor ailments can be considered healthy. However the issue here is that subjects presenting with, or being treated for, a disease can be included in a trial simply by virtue of the fact that the doctor has them " at hand" and reliant on him/her. This possibility cannot be dismissed. If the trials are to be conducted on dependants of the instigator or of the person in charge of the research, or on medical students, this fact must be mentioned in the protocol submitted to the ethical review committee.

Consent to trials of this type is a " trial contract" . It must be subject to a written agreement signed by both parties. Not only must the agreement provide all the required information, but also detail the obligations of each party; furthermore, it must stipulate the mode of payment and, as the case may be, the amount payable to the volunteer. This amount can be nothing more than compensation for the inconvenience suffered. No financial reward may be paid. Thus, the amount payable can not be taken as an incentive to encourage participationsince trials of this nature are ethically justified only if the volunteer wishes to further medical science through the commitment she/he has made. Volunteers should be informed of the outcomes of the trial in which they take part. To cover any injury attributable to the trial, the instigator must take out insurance.

5) Examination by an ethical review committee

No trials on healthy volunteers can be performed without the favourable opinion of the ethical review committee. The committee must ensure that the four obligations set out above have been strictly observed. Verification is in the order stipulated herein. If one condition is not met, the subsequent conditions are not examined. Additionally, the comparison of the viewpoints of people from different backgrounds is vital at this point given the novelty and unusual subtlety of experimentation on healthy volunteers.

C) Role of trials in therapeutic advances. Review and outlook.

1) For some diseases, it would be worthwhile to set up a permanent structure to evaluate the role played by trials in the advancement of therapy. There is such an international structure for cancer. Since 1967, the therapeutic trials bureau of the International Union Against Cancer (l'Union internationale contre le cancer), located in France has recorded right from their start almost all the tests and trials run throughout the world. Hence, it can be seen how many have given rise to changes in therapy and how long it took for the changes to come about. A similar recording system should be used for other sicknesses. These records have another advantage: they also show which trials have given negative results, and which often go unpublished. They are essential to any review of outcomes. Furthermore, one method steadily gaining currency is to collate the results of trials from all

over the world. Indeed, this is a productive approach; but of course it is valid only if negative results are included.

2) At all events, trials certainly could play a more important role than is currently the case. Progress requires training and information: training of people to carry out trials properly; wide publication of the outcomes; and, preparation of doctors so that they can make a critical selection of trials and promptly adopt the treatments which pass the test.

Appendix 1 : Some of the difficulties encountered in therapeutic trials

The methodology used in controlled therapeutic trials is a subject in itself and has been dealt with in books and courses. The purpose of this appendix is to show how numerous errors can occur and render the conclusions of the trial either completely unusable or erroneous. Such errors can involve very subtle aspects of reasoning and could very well be made by a non-specialist; for example:

1) Formulation of the question

Trials are sometimes conducted under conditions of treatment administration and/or monitoring of patients so stringent that they cannot be reproduced in normal practice, whereas the aim is to test the effects of the treatment in normal practice. In this case, the conclusions of the trial are altogether unusable. Generally speaking, the conclusions from a trial are valid only for the conditions under which the trial was conducted. This goes to show how vital it is to thoroughly determine, and specify in the protocol, the mode of treatment administration, the type of patient selected, the and way in which they are monitored - all of which demand a very clear formulation of the issues.

2) The ambivalence clause

Some subjects may present a contra-indication detectable from the outset to one of the treatments. If they are to take part in the trial and are put into the group which receives this treatment, they must be excluded. However, these subjects are perhaps different from the others and so their removal could change the profile of the group thereby compromising the comparability achieved initially. To avoid such a mistake, only those subjects displaying no contra-indications to either of the treatments can be included in the trial. The test population then runs the risk of being slightly different from the general population of patients; but it is the population of patients able to receive one or the other treatment; and this is precisely the population to which the issue of the comparison applies.

3) The Size of the subject cohort

If there are too few subjects per group, results will have a wide margin of error and it will be more difficult to tell which is the better treatment. For the trial to be valid, a certain number of patients is needed; it can be calculated by statisticians. The minimum number to ensure validity must be stipulated and explained in all protocols.

4) Analyses during the trial

When possible, it is tempting to review results at various points, and perhaps continuously; and to end the trial as soon as a significant difference appears. This approach, which increases the likelihood of detecting a chance deviation, is flawed if unaccompanied by an appropriate change in the statistical analysis.

5) Analysis by sub-groups

When the analysis has to be made, there might be a temptation to compare the outcomes

of the two groups - not only as a whole, but also on the basis of sex, age, clinical manifestations, and so on. The more such comparisons are made the greater the chance of observing a fortuitous variance, which can lead to false conclusions if the correct methods have not been applied.

6) Data quality

That data quality is a must goes without saying, but it is better said nonetheless. In fact, it is often thought that the sophistication of the statistical analysis and/or the power of the computing resources will compensate for any shortcomings of data. This is the first mistake to avoid. Nothing good can ever come of poor data.

Appendix 2 : Incompetents (trials on patients or subjects at risks)

Minors and legally incompetent majors adults protected by court order.

I. Minors

A - Unemancipated minors

They are under the authority of their father and mother who are to ensure their safety, health, and morality (article 371/2 of the code of civil law). Consequently, consent must be requested from both parents who while married " shall exercise their authority jointly" (article 372 of the code of civil law). Should the parents be divorced, the mode in which consent is obtained is subject to the rulings concerning parental authority handed down by the magistrate.

If the child is placed in guardianship, consent has to be sought from the board of guardians (article 449 of the code of civil law).

B - Emancipated minors

They are considered to be of age (article 481 of the code of civil law) except in two cases: to marry or to offer themselves for adoption.

It must be noted that once the minor is no longer an infant he/she can give legally valid consent just like an adult. Information to the minor on the treatment envisaged must not be neglected any more than it should for a person of full age; however, because of age, the minor's consent is not sufficient: it is not considered sufficiently free and informed. Nonetheless, the minor's refusal to undergo the treatment must be taken as an inviolable barrier.

II. Incompetent Adults Protected by Court Order

These are people whose mental faculties are impaired thereby making it impossible for them to attend to their own welfare (article 488 al. of the code of civil law). This shows that the problem they pose is very different from that of minors. Their consent is to varying degrees neither free nor enlightened. Consequently, the weight of the decision in regard to consent lies largely with the legal guardians.

Legal provision has been made for three systems to ensure the protection of such persons: legal protection by petition to the Procureur de la République, wardship, and guardianship.

Consent to the trial must be obtained from the legal guardians in accordance with

procedures which depend on the different entities involved: the judge supervising the guardianship, the guardian, or the board of guardians.

Regulations to be enacted on this matter must be just as discriminating as the existing instruments; hence the consent of the person directly concerned cannot be excluded in all cases. Suffice it to say that spendthrifts are included in this category (article 488 of the code of civil law) as are adults who are wards of the state of whom article 508 of the code of civil law states that they are not incapable of acting for themselves. Such subjects as these are lucid enough to be involved in the decision.

Appendix 3 : Proposals on the creation and opeartion of ethics committees

Ethics committees should be created by official provisions, with the onus on the instigator of a trial to obtain the opinion of a committee.

This obligation can easily be decreed within the framework of trials on drugs, and possibly by making an addition to the regulations on the AMM (authorisation to market, or autorisation de mise sur le marché).

Extending this to non-medicinal experimentation is more troublesome: it is difficult to see how the comparison of two surgical procedures, for instance, could fall within a regulation as - contrary to drugs - no government authorisation is required for their application. However, it may be surmised that the introduction of such an obligation in relation to drugs would be a strong incentive to do likewise for non-drug trials.

The obligation should apply not only to stage 3 trials - which are those most often submitted to the as yet unofficial ethical review committees, but also to stage 1, stage 2, and stage 4 trials.

The opinion of the ethical review committee should handed down quickly as trials can not be held up by bureaucracy. A maximum time limit must be set (six weeks?). Provision must be made for some sanction of the ethical review committee if it does not respond within the required time, which is not to be taken either as a favourable or an unfavourable opinion; for instance, the ethical review committee might be dispossessed of the case, which would them go before the national ethical review committee.

The opinions of the ethical review committees can be challenged before the national ethical review committee. It is highly desirable for the deliberations of the ethical review committee considering the merits of a trial to be unequivocal, so as to rule out any choice and to prevent a request being made to several committees at once. The best solution would appear to be to partition the country into zones each with one committee. The " promoter" or instigator of a trial would have to apply to the committee of his/her zone. A " zone" could be an administrative area, a group of administrative areas (if the volume of work is small), or a subdivision of an administrative area. The advantage of this arrangement is that it would ensure committee rulings were unequivocal. Even for a multicentric study, there would be no alternative: there is always one and one only instigator per trial and the relevant committee would that of his/her zone. Committees should be set up gradually and take into account certain ethical review committees already in existence. Another solution might be to draw up a list of authorised ethical review committees, with a choice given to the instigator, whose choice would have to be justified on geographical or other grounds. The can be informed and intervene if difficulties arise; however, this solution - which does not ensure unequivocal deliberations - must only be considered with serious reservations.

In all events, co-ordination must be instituted among the various ethical review committees at all levels. This could be carried out by the national committee.

The membership and establishment of the committees must be determined by official documents which set forth some of the rules but leave room for flexibility in their application. As to membership, each committee will have to include at least specialists in therapeutic trials and clinical pharmacology, jurists (if possible a magistrate and an academic), pharmacists, nurses, researchers, possibly users of the health system, of course a sufficiently large number of clinicians, and one or two people from outside the region. The task of putting the committees together could be entrusted to a small number of distinguished people such as the dean of the school of medicine, of the president of the university, the managing director of hospitals, an authority from the Conseil de l'Ordre (governing body of France's medical association), the highest judicial authority, and a few others to be decided upon. They would propose members in accordance with the rules of membership defined herein. Their appointment would have to be confirmed by a higher body. Members would be chosen for their competence but also depending on their availability (which would have to be considerable).

Indeed, the ethical review committees should not only be involved with the evaluation of trials for curative, preventive, and diagnostic purposes though this work will take up most of their time: it is reasonable to consider that the committees will have to examine all the moral issues raised by all research into biology, medicine, and health - otherwise there would be a profusion of committees.

The preceding proposals should be broadened to cover these aspects, especially committee membership.

No attempt should be made to hide from the fact that for such committees, the many members of which are often scattered over a region, to swing into operation both quickly and efficiently adequate finance will be required.

Appendix 4 : Principal national and international declarations

I. Declarations of Nuremberg, Helsinki-Tokyo, and Manila

The Nuremberg Code, 1947

1. The voluntary consent of the human subject is absolutely essential.

This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without intervention of any element of force, fraud, deceit, duress, over-reaching or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject, there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs, or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another without impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except perhaps in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment, the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment, the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Declaration of Helsinki

Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and as revised by the 29th World Medical Assembly in Tokyo, Japan in 1975.

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, " The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, " A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I - Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the

discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, permission from the responsible relative replaces that of the subject in accordance with national legislation.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II - Medical Research Combined with Professional Care (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. 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.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee I.2.

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III - Non-Therapeutic Biomedical Research

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers--either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

International Ethical Guidelines for Biomedical Research

Involving Human Subjects

A joint project of the World Health Organisation and the Council for International Organisations of Medical Science - Manila, 1981.

Preamble

All advances in medical practices are dependent upon an understanding relevant physiological and pathological processes and must necessarily, in the last resort, be tested for the first time on human subjects. It is in this sense that the term " research involving human subjects" is used.

The context in which such research is undertaken is wide and includes:

- studies of a physiological, biochemical, or pathological process, or of the response to a specific intervention - either physical, chemical, or psychological - in healthy subjects or patients under treatment;

- prospective controlled trials of diagnostic, prophylactic, or therapeutic measures in larger groups of patients, with a view to demonstrating a specific response against a background of individual biological variation;

- studies in which the consequences of specific prophylactic or therapeutic measures are determined within communities;

Research involving human subjects is thus defined for the purposes of these guidelines as:

any study involving human subjects and directed to the advancement of biomedical knowledge, that cannot be regarded as an element in established clinical management or public health practice and that involves either:

- physical or psychological intervention or assessment; or,

- generation, storage, and analysis of records containing biomedical information referrable to identifiable individuals.

Such studies include not only planned interventions on human subjects but research in which environmental factors are manipulated in a way that could place incidentally-exposed individuals at risk.

The terms of reference are framed broadly, in order to embrace field studies of pathogenic organisms and toxic chemicals under investigation for medical purposes. Analogous risks are recognised to arise in research directed to other objectives but non-medical research does not fall within the scope of this document.

Research involving human subjects should be carried out only by appropriately qualified and experienced investigators in accordance with an experimental protocol that clearly :

- states the aim of the research;

- the reasons for proposing that it should be undertaken on human subjects; - the nature and degree of any known risks;

- the sources from which it is proposed that subjects should be recruited;

- and the means proposed for ensuring that their consent is adequately informed.

The protocol should be scientifically and ethically appraised by a suitably constituted review body independent of the investigators.

The guidelines proposed below will offer some countries nothing which is not already in force in one form or another. They have been framed with special reference to the requirements of developing countries and elaborated in the light of replies to a questionnaire received from 45 national health administrations and 91 medical faculties in countries in which medical research involving human subjects is as yet undertaken on a limited scale and/or in the absence of explicit national criteria for protecting such subjects from involuntary abuse. The replies were received from a total of 60 developing countries.

International declarations

1. The first international declaration on research involving human subjects was the Nuremberg Code of 1947, which was a by-product of a trial of physicians for having performed cruel experiments on prisoners and detainees during the Second World War. The Code lays particular stress on the " voluntary consent" (" informed consent" is now the usual term) of the subject which is stated to be " absolutely essential" .

2. In 1964, the World Medical Association (WMA), at its 18th World Medical Assembly, adopted the Declaration of Helsinki (" Helsinki I")which was a set of rules to guide physicians engaged in clinical research, both therapeutic and non-therapeutic.

At its 29th World Medical Assembly, the WMA revised this Declaration (" Helsinki II"), broadening its scope to include " biomedical research involving human subjects" . Some important new provisions in the revised Declaration were that experimental protocols for research involving human subjects " should be transmitted to a specially appointed independent committee for consideration, comment, and guidance" (article I, 2); that such protocols should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with (article I, 12); and that reports on " experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication" (article I, 8).

3. Both the Nuremberg Code and the original Declaration of Helsinki of 1964 have been superseded by " Helsinki II" , the full text of which is appended. This is the basic document in its field and has been widely accepted as such.

4 These guidelines take account of the distinction made in " Helsinki II" between medical research combined with professional care (clinical research) and non-therapeutic (non-clinical) biomedical research.

5. While the general principles laid down in " Helsinki II" may be regarded as of universal validity, their modes of application in various special circumstances must necessarily vary. The purpose of the present guidelines is therefore not to duplicate or amend these principles, but to suggest how they may be applied in the special circumstances of many technologically developing countries. In particular, the limitations of the informed consent procedure are emphasised, and issues specific to research involving communities rather than individual subjects are addressed.

Consent of subjects

6. " Helsinki II" requires (article I, 9) that human subjects should not be used in medical research unless " freely-given, informed consent" has been elicited after having been adequately informed of the " aims, methods, anticipated benefits, and potential hazards" of

the experiment and informed that they are free to abstain or to withdraw from participation at any time. Of itself however, informed consent offers an imperfect safeguard to the subject and it should always be complemented by independent ethical review of research proposals. Moreover, there are many individuals including children, adults who are mentally ill or defective, and those who are totally unfamiliar with modern medical concepts who are incapable of giving adequate consent and from whom consent implies a passive and uncomprehending participation. For such groups in particular, ethical review is imperative.

Children

7. It is axiomatic that children should never be the subjects of research that might equally well be carried out on adults. However, their participation is indispensable for research on diseases of children and conditions to which children are particularly susceptible. The consent of a parent or other legal guardian after a full explanation of the aims of the experiment and of possible hazards, discomfort, or inconvenience, is always necessary.

8. To the extent that it is feasible, which will vary with age, the willing co-operation of the child should be sought after it has been frankly informed of any possible discomfort or inconvenience. Older children may be assumed to be capable of giving informed consent, preferably also with the consent of the parent or other legal guardian.

9. Children should in no circumstances be the subject of research holding no potential benefit for them unless with the objective of elucidating physiological or pathological conditions peculiar to infancy and childhood.

Pregnant and nursing women

10. While no special problems of eliciting informed consent exist in the case of pregnant and nursing mothers as such, they should in no circumstances be the subjects of non-therapeutic research that carries any possibility of risk to the foetus or neonate unless this is intended to elucidate problems of pregnancy or lactation. Therapeutic research is permissible only with a view to improving the health of the mother without prejudice to that of the foetus or nursling, to enhancing the viability of the foetus, or to aiding the nursling's healthy development or the ability of the mother to nourish it adequately.

Research directed to induced termination of pregnancy, or undertaken in anticipation of termination is an issue that is dependent upon national legislation, and religious and cultural precepts and therefore does not lend itself to an international recommendation.

Mentally ill and mentally defective persons

11. Substantially similar ethical considerations apply to the mentally ill and mentally defective as to children. They should never be the subjects of research that might equally well be carried out in adults in full possession of their intellectual faculties, but they are clearly the only subjects available for research into the origins and treatments of mental disease and disability.

12. The agreement of the immediate family, whether spouse, parent, adult offspring, or sibling should be sought, but is sometimes of doubtful value as mentally deranged or defective patients are sometimes regarded by their families as an unwelcome burden. Where a subject has become compulsorily committed to an institution by a court order, it may be necessary to seek legal sanction before involving the subject in experimental procedures.

Other vulnerable social groups

13. The quality of the consent of candidate subjects who are junior or subordinate members of a hierarchically-structured group requires careful consideration, as willingness to volunteer may be unduly influenced by the expectation, whether justified or not, of adventitious benefits. Examples of such groups are medical and nursing students, subordinate laboratory and hospital personnel, employees of the pharmaceutical industry, and members of the armed forces.

Subjects in developing countries

14. Rural communities in developing countries may not be conversant with the concepts and techniques of experimental medicine. It is in these communities that diseases not endemic in developed countries exact a heavy toll of illness, incapacity, and death. Research on the prophylaxis and treatment of such diseases is urgently required, and can be finally carried out within the communities at risk.

15. Where the individual members of a community do not have the necessary awareness of the implications on the participation in an experiment to give adequately informed consent directly to the investigators, it is desirable that the decision whether or not to participate should be elicited through the intermediary of a trusted community leader. The intermediary should make it clear that participation is entirely voluntary, and that any participant is free to abstain or withdraw at any time from the experiment.

Community-based research

16. Where research is undertaken on a community basis - for example by experimental treatment of water supplies, by health services research or by large-scale trials of new insecticides, of new prophylactic immunising agents and of nutritional adjuvants or substitutes - individual consent on a person-to-person basis may not be feasible, and the ultimate decision to undertake the research will rest with the responsibility of the public health authority.

17. Nevertheless, all possible means should be tried to inform the community concerned of the aims of the research, the advantages expected from it, and any possible hazards and inconveniences. If feasible, dissenting individuals should have the option of withholding their participation. Whatever the circumstances, the ethical considerations and safeguards applied to research on individuals must be translated in every possible respect to the community context.

Review procedures

18. The provisions for review of research involving human subjects are influenced by political institutions, the organisation of medical practice and research, and the degree of autonomy accorded to medical investigators. Whatever the circumstances however, a dual responsibility exists within society to ensure that :

- all drugs and devices under investigation in human subjects meet adequate standards of safety;

- the provisions of " Helsinki II" are applied in all biomedical research involving human subjects.

Assessment of safety

19. Authority to assess the safety and quality of new medicines and devices intended for

use in man is most effectively vested in a multidisciplinary advisory committee operative at the national level. Clinicians, clinical pharmacologists, toxicologists, pathologists, pharmacists, and statisticians have important contributions to offer these assessments. Many countries at present lack resources to undertake independent assessments of technical data according to procedures and standards now considered mandatory in many highly developed countries. Improvement in their capability to subserve this function is dependent, in the short term, on more efficient exchange of relevant information internationally.

Ethical review committees

20. It is not possible to draw a clear dividing line between scientific review and ethical review for an experiment on human subjects that is scientifically unsound is ipso facto unethical in that it may expose the subjects to risk and inconvenience to no purpose. Normally, therefore, ethical review committees consider both scientific and ethical aspects. If a review committee finds a research proposal scientifically sound, it will then consider whether any known or possible risk to the subject is justified by the expected benefit and, if so, whether the proposed procedure for eliciting informed consent is satisfactory.

21. In a highly centralised administration, a national review committee may be constituted to review research protocols from both scientific and ethical standpoints. In countries where medical research is not centrally directed, protocols are more effectively and conveniently reviewed from the ethical standpoint at local or regional level. The basic responsibilities of locally operative ethical review committees are two-fold :

- to verify that all proposed interventions, and, particularly, the administration of drugs under development, have been assessed by a competent expert body as acceptably safe to be undertaken in human subjects.

- to ensure that all other ethical considerations arising from a protocol are satisfactorily resolved both in principle and in practice.

22. Review committees may be created under the aegis of national or local health administrations, of national medical research councils, or of other nationally-representative medical bodies. The competence of committees operating on a local basis may be confined exclusively to a specific research institution, or it may extend to all biomedical research involving human subjects undertaken within a defined geographical area.

23. Local review committees act as gatherings of the investigators' peers and should be so composed as to provide complete and adequate review of the research activities referred to them. The membership may include other health professionals, particularly nurses, as well as laymen qualified to represent community, cultural, and moral values. Independence from the investigators is maintained by precluding any member with a direct interest in a proposal from participation in its assessment.

24. The requirements of review committees should be particularly stringent in the case of proposed research involving children, pregnant and nursing women, members of developing communities unfamiliar with modern clinical concepts, and any invasive, non-therapeutic research.

Information to be provided by investigators

25. Whatever may be the pattern of the procedure adopted for ethical review, it should be based on a detailed protocol comprising :

- a clear statement of the objectives having regard to the present state of knowledge and a justification for undertaking the investigation in human subjects

- a precise description of all proposed interventions, including intended dosages of drugs and planned duration of treatment;

- a statistical plan indicating the number of subjects to be recruited and the criteria for terminating the study;

- the criteria determining admission and withdrawal of individual subjects including full details of the informed-consent procedure.

26. There should also be included information to establish :

- the safety of each proposed intervention and of any drug or device to be tested, including the results of relevant laboratory and animal research;

- the presumed benefits and potential risks of participation;

- the means proposed to elicit informed consent or, when this is not possible, satisfactory assurance that the guardian or family will be appropriately consulted and the rights and welfare of each subject will be adequately protected;

- evidence that the investigator is appropriately qualified and experienced, and commands adequate facilities for the safe and efficient conduct of the research;

- provisions that will be made to protect confidentiality of data;

- the nature of any other ethical considerations involved together with an indication that the principles enunciated in " Helsinki II" will be implemented.

Externally sponsored research

27. The term externally sponsored research is here used to refer to research undertaken in a host country but initiated, financed, and sometimes wholly or partly carried out by an external international or national agency with the collaboration or agreement of the appropriate authorities of the host country.

28. Such research implies two ethical imperatives :

- the research protocol should be submitted to ethical review by the initiating agency. The ethical standards applied should be no less exacting than they would be for research carried out within the initiating country;

- after ethical approval by the initiating agency, the appropriate authorities of the host country, should, by means of an ethical review committee or otherwise, satisfy themselves that the proposed research meets their own ethical requirements.

Where externally sponsored research is initiated and financed by a pharmaceutical manufacturer, it is in the interest of the host country to require that is should be submitted with the comments of a responsible authority of the initiating country such as a health administration, research council, or academy of medicine or science.

29. An important secondary objective of externally sponsored research should be the training of health personnel of the host country to carry out similar research projects independently.

Compensation of research subjects for accidental injury

30. Reports of accidental injury to subjects volunteering to participate in therapeutic or non-therapeutic research and resulting in temporary or permanent disability, or even death, are excessively rare. In fact, human subjects of medical research are usually in exceptionally favourable circumstances in that they are under close and continued observation by highly qualified investigators who are alert to detect the earliest signs of untoward reaction. Such conditions are less likely to occur in routine medical practice.

31. However, any volunteer subjects involved in medical research who may suffer injury as a result of their participation are entitled to financial or such other assistance as would compensate them fully for any temporary or permanent disability. In the case of death, the dependants should be eligible for appropriate material compensation.

32. Experimental subjects should not, in giving their consent to participation, be required to waive their rights to compensation in the case of an accident, nor should they be required to show negligence or lack of a reasonable degree of skill on the part of the investigator. Support is increasing for a system of insurance against risks, financed either by public or private funds or both, the injured party having only to show a causal relationship between the investigation and his injury. For research sponsored by pharmaceutical manufacturers, the manufacturers themselves should assume responsibility in case of accidents. This is particularly necessary in the case of externally sponsored research when the subjects are not protected by social- security measures.

Confidentiality of data

33. Research may involve the collection and storage of data relating to individuals which if disclosed to third parties might cause harm or distress. Consequently, arrangements should be made by investigators to protect the confidentiality of such data, as for example by omitting information which might lead to the identification of individual subjects, by limiting access to the data, or other appropriate means.

II. Excerpts from Comments to Article 19 of the Code of Ethics adopted by Conseil National de l'Ordre, 28 January, 1983

- " Before any new medicine can be disseminated, experimentation on humans is absolutely necessary. It is to be preceded by scientific laboratory and animal studies...

- Such experimentation on human beings is even a moral obligation; for it is reprehensible to suggest that little-known drugs be used of which the sometimes serious side effects would only become known after calamity has struck...

- It is vital that such trials be conducted with the fullest scientific rigour.

Scattered, empirical trials involving a small number of cases which leave it to chance to inform us too late of the dangers and set-backs cannot be allowed...

- On the condition that very strict rules of precaution be observed, experimentation on healthy subjects is less disturbing than that practice which consists of using patients - unbeknown to them - to test substances of no potential benefit to them....

- The subjects (2) chosen must be consenting volunteers... No coercion, threat, or enticement with gain in nature or in kind is acceptable" .

Notes

1. For convenience, such actions, including work on diagnosis, will be termed "treatments"

2. Healthy volunteers

NB This document was written by a working party and submitted to the National Ethics Consultative Committee