Advisory Committee on Bioethics

INTRODUCTORY REPORT FOR OPINION No 13 of 9 July 2001 on human experimentation

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A. OBJECTIVES AND METHOD

Ethical reflection on a given activity (in this case, human experimentation) involves thinking about the *objectives* of this activity and studying the extent to which these objectives benefit human beings or not: what advantages and hopes do the experiments bring, but what are the risks? (Part C, below). In this way, we can form an idea of the *values* we want to achieve.

By analysing objectives and values, it is possible to determine our *expectations* as regards those involved in the experimentation, the *attitudes* needed and *ethical requirements* that this type of activity should fulfil.

Examining attitudes and requirements will result in a *debate* on the issue of whether a *normative framework* relating to human experimentation is desirable and even necessary (Part E). This normative framework, made up of *ethical*, *deontological* and *legal rules*, may provide indications on how to proceed when carrying out human experimentation so as to guarantee its ethical quality.

The debate on a normative framework seeks to fulfil a twofold objective: on the one hand, to make clear what are the ethical standards relating to the experimentation regarding which a consensus can be reached within the Advisory Committee; on the other hand, to indicate the extent to which the ethical requirements and standards to be met by the various players have to be established by legal rules.

B. DEFINITIONS

Ethical reflections, the analysis of objectives and values and the formulation of standards for a specific activity assume the use of clear and correct concepts.
When establishing its own key concepts, the Advisory Committee took inspiration from the following:

1. the Declaration of Helsinki adopted by the World Medical Association in June 1964 (amended in Tokyo in October 1983, then in Hong Kong in September 1989, in Somerset West (Republic of South Africa) in October 1996 and finally in Edinburgh in October 2000),
2. the *Dictionnaire Permanent de Bioethique*, Ed. Legislatives, Montrouge, France,
3. the Encyclopedia of Applied Ethics, Editor CHADWICK, R., 4 volumes, Academic Press, USA, 1998
4. the Guidelines for Good Clinical Practice (G.C.P.) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH),
5. European Directive 2001/20/EC of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (O.J. 1 May 2001), and
6. Article ATLAN, H., "Distinctions necessaires: l'innovation therapeutique, l'expérimentation sur l'adulte, l'expérimentation sur l'embryon", in the collective work "*Expérimentation biomédicale et Droits de l'Homme*", PUF, Paris, 1988.

The central concept is that of experimentation.

Experimenting means *submitting to a scientific test*. The researcher starts from an assumption and wants to see whether, when confronted with the facts, this assumption is confirmed or invalidated.
The objective of experimentation is the *acquisition of general knowledge* that is beneficial to the community and to humanity. The means used to achieve this objective is the *experimental strategy*.
This report is confined to human experimentation: this is referred to by the terms: *experimentation subject, trial subject* or *subject*.
It was decided to defer until a subsequent examination the practical situations that require special precautions owing either to the vulnerability of individual or the impossibility of obtaining informed consent, as expressed in the opinion.

All experimentation in the medical field pursues a cognitive objective, as it always aims to acquire new knowledge. Consequently, there is always a cognitive objective alongside any benefit for the trial subject.
However, some members of the Advisory Committee deem it useful to recall the distinction often made between cognitive experimentation, non-therapeutic experimentation and therapeutic experimentation.
The sole aim of *cognitive experimentation* is to improve the state of knowledge and it is not, in principle, of any immediate interest for the trial subjects.
Non-therapeutic experimentation has no therapeutic objective as regards the trial subjects and is therefore ultimately synonymous with cognitive experimentation. In this case, the trial subjects are often (but not always) volunteers in good health.
Therapeutic experimentation aims to advance scientific knowledge by testing a treatment, diagnostic or prevention process on individuals who are likely, at the same time, to benefit directly in terms of their state of health.
Other members reject these distinctions: they stress that as the objective of experimentation is always advance knowledge, all experiments are for cognitive purposes[1]. The "therapeutic-cognitive" distinction will not be discussed any further here.

Therapeutic innovation (also known as *new therapy or experimental therapy*) is not experimentation. It involves treating an individual patient using a new method or a new medicinal product and its objectives are no different from those of ordinary therapy: it is not necessary to draw up an experimental protocol, the patient is not a trial subject and the ultimate aim of the treatment remains exclusively the patient himself and his personal well-being. In fact, the question here concerns the legitimacy of the medical intervention.

The Advisory Committee feels it is important to keep in mind the successive phases of biomedical experimentation concerning *potential medicinal substances* as they show in exemplary fashion the complexity of an experimentation procedure. They thus make it possible to be aware of the ethical and legal problems that arise.

This type of experimentation begins with laboratory studies, for example in the form of trials

[1] These members consider that the distinction between therapeutic experimentation and non-therapeutic experimentation is ultimately not decisive because in both cases, since it is a matter of experimentation, the cognitive objective takes precedence. From this point of view, a therapeutic objective which is added to the cognitive objective of an experiment can only ever be considered a secondary objective; under no circumstances does it annul or attenuate the experimental (and therefore primarily cognitive) nature of the procedure undertaken.

on animals, which in principle make it possible to study the evolution and effects of the product in a living organism.

This is followed by clinical studies which consist of four successive phases.
Phase I involves administering the product for the first time, in principle to a small number of volunteers in good health, in order to assess their tolerance to the product, determine the maximum dose tolerated by humans and the minimum active dose of the product, and study its pharmacokinetic and pharmaco-dynamic properties.
Phase II concerns trials on a limited group of patients suffering from the pathology for which the product is intended, in order to confirm its efficacy, assess its therapeutic interest, evaluate the relationship between the risks and the advantages linked to its administration and seek the best dose and the best means of administration depending on the effect sought.
During phase III, studies are conducted on a large number of patients, usually divided into comparable groups according to a strict methodology (randomisation). These studies aim to examine tolerance in the medium term and efficacy, so as to be able to estimate the relationship between the benefits and the disadvantages (unwanted effects and cost). This phase is also used to gather information which will be useful for prescribers. If it proves conclusive, the next step is to think about marketing the product and fulfilling the procedures required to obtain authorisation to place it on the market.
Phase IV comprises the studies conducted once the product has been put on the market. These studies enable better knowledge of the product: the possible association with other therapies, the discovery of new actions, the rare or belated side effects, etc.

It should be remembered that the concept of human experimentation is far broader than that of pharmaco-therapeutic experimentation. Without claiming to be exhaustive, it includes the fields of physiology and physiopathology; it may also concern screening and diagnosis techniques, or involve the assessment of new devices or non-medicinal treatments: new techniques, medical appliances, psychotherapy, for instance.

In addition to the principle concept of *experimentation*, the following key concepts also require explanation.

The *trial subject* is the person who, alone or as part of a group, takes part in the experiment and whose organism or mind is the subject of the research.

The *experimenter or investigator* is the person in charge of conducting the clinical study. When the study is carried out by a team of people, an investigator is the head or leader of this team, in charge of the team as a whole. He is referred to as the *principal investigator*.

The sponsor or *body subsidising the study* is the person, the company, the institution or the body that takes responsibility for devising, managing and funding the clinical study.

The *experimental protocol* is a document that describes, in particular, the objectives, the procedure, the methodology, the statistical elements and the organisation of the study. The experimental protocol also usually explains the foundations of and justifications for the study, even though this information may also appear in other documents to which reference is made in the experimental protocol.

A *placebo* is a tablet, an injection or a treatment which the trial subject believes will have an effect (positive or negative) on his state of health and which, owing to this conviction on the part of the person concerned, can actually have such an effect, but which the investigator is

convinced is inert vis-à-vis the state of the trial subject.

When, in the context of any experiment during which a treatment is compared to an acknowledged existing treatment or a placebo, one or several of the parties concerned are kept in ignorance of the allocation of treatments to the trial subjects (e.g. the active treatment or the placebo), this is known as a *blind study*. The experiment is *single blind* when only the trial subjects are not informed; it is *double blind*) when the investigator, his team, the supervisor and, in some cases, the data analyst or analysts are also unaware which subject is given which treatment.

Basic research is research during which phenomena are studied with a view to improving scientific knowledge, but without any direct intention of applying this knowledge in practice.

Applied research, on the other hand, involves experimentation where the objective is to apply the scientific knowledge acquired to practical situations such as illnesses.

Randomisation is the use of chance to determine the allocation of trial subjects to treatment or control groups; the aim here is to reduce bias which may distort the conclusions.

The *control treatment* is the better medical treatment or the usual medical treatment for a patient or, for instance if there is no such treatment, the placebo treatment with which the experimental treatment is being compared.

Bias is the term used if a systematic error is observed in the experimental protocol that is likely to have led to distorted conclusions.

An experimentation protocol must be submitted to a *local ethics committee* for an opinion. A local ethics committee is understood here to refer to the local ethics committees instituted by Article 70 *ter* of the act of 7 August 1987 on hospitals (inserted by Article 194 of the act of 25 January 1999, *Moniteur belge* (Belgian official journal) of 6 February 1999). The Advisory Committee points out that, as regards its advisory mission, the local ethics committee has a twofold task of ‘assessment and supervision of the research’.
In the context of this report, the term used will be ‘ethics committee’.

C. MEDICAL-SCIENTIFIC RESEARCH ON HUMANS – ETHICAL AND LEGAL PROBLEMS

1. LEGITIMACY BASED ON EFFICACY

The history of experimentation in medicine coincides with the gradual learning of how to experiment on human subjects appropriately, both in terms of methodology and from an ethical point of view. The use of human experimentation is only justified in cases of clinical uncertainty.
Little by little, experimental methods have become more refined: comparative experiment, experimental plan, randomisation of patients assigned to the 'treated' group and the 'control' group, use of placebos, double-blind method, statistical calculations, etc. These experiments, properly conducted scientifically, are far more fruitful in terms of advancing knowledge than the simple empirical trial and error approaches of previous centuries. We therefore have a duty to experiment in order to provide patients with better knowledge and better treatments**.**

2. CARE AND RESEARCH

Experimentation radically transforms medicine. Medicine itself is no longer seen exclusively as the art of curing. The aim is for this art, which remains its main objective and nature, to be able to rely on scientific knowledge, acquired through experimentation, of the human body, its illnesses, and diagnostic and therapeutic means. By doing so, it is divided into two fields of activity: care and research.
These differ from one another in the immediate objectives pursued: care on the one hand, contribution to scientific knowledge on the other. Fulfilling these objectives requires the implementation of separate procedures. In fact, the abundance of features common to therapeutic acts, in particular those considered 'experimental', and to experiments (whether therapeutic or not) undertaken for the purpose of research cannot hide the fact that they are part of separate processes. An act undertaken mainly for therapeutic purposes is controlled by the characteristics of the patient, which may lead the doctor to diverge from standard practice in the hope of achieving greater efficacy. This is therefore essential a practical procedure: it involves seeking to obtain the best effect for a given patient. Two features should be noted: this type of act is intended for a given person; it seeks above all to achieve an effect. The act of experimental care is therefore identified with the therapeutic relationship. Experimentation undertaken for cognitive purposes may also, where appropriate, be polarised by the search for an effect. However, it differs from the act of 'experimental' care because it is part of an experimentation plan that aims to test an assumption, usually by means of a trial involving a group of people. To do this, a situation is devised and created in which variables deemed to be relevant will be monitored as rigorously as possible. Experimentation consists of introducing variations – which are also monitored – into this situation. The results are collected and interpreted; they are used to see whether the initial assumption can or cannot be confirmed. Consequently, there are differences, induced by the pursuit of different objectives. The important thing to remember is that 'good' scientific experimentation presupposes strict compliance with experimentation plan drawn up beforehand, whereas the act of experimental care requires constant adjustment to the needs of the patient.
Separate procedures have to be planned with regard to ethics, deontology and the law, as they involve specific modalities in the relationship with patients, as with individuals in good health.

The distinction between care and research is difficult to establish for a number of reasons. The procedures relating to the one or the other are indiscernible in material terms: same players,

same places, often the same acts and sometimes the search for an effect in both cases. They are all marked by uncertainty; moreover in both cases, the term used is trial. They are very closely intertwined: practice stimulates and extends research. Finally, they share an ultimate objective: to improve knowledge, relieve suffering and restore health.

The difficulty of establishing this distinction leads to the risk of concealing it behind the ultimate therapeutic objective, which is common to all medical activities. This risk is all the greater as the doctor is obliged to provide care "in line with current scientific data". Consequently, from his point of view, there is a constant exchange between care and research, or even a continuum: experimentation appears as the most rigorous means of acquiring experience, of becoming an experienced doctor, that is a doctor who has practised a great deal and has learnt lessons from his practising[2].

If doctors sense a close connection between care and research, this results from the collaboration between activities with separate epistemological statuses which, for this reason, involve specific modalities as regards the relationship with patients, when they are also trial subjects.
Maintaining the distinction between care and research is therefore vitally important and makes it possible to avoid unsound compromises in both epistemological and moral terms. This does not mean, however, that the qualities required when exercising either of these activities are mutually exclusive. For instance, the attention paid to people – which is expected to be of paramount importance in the context of care – must also underlie and motivate experimental activities even if, in this context, it has to be combined with and often be overshadowed by the requirements of clinical research. However, being overshadowed does not mean disappearing. It means being removed from view, while remaining present. Conversely, care given without scientific competence is unacceptable in every respect.

3. THE CULTURAL CONTEXT

Current consideration of human experimentation is taking place in a cultural context marked by the tension between the affirmation of principles expressing the acknowledged value of individuals as such (human rights) on the on one hand and principles that link the morality of an action to a rational calculation of utility and emphasise the collective good on the other. Excessive preference for the common good could lead to neglect of the rights of the individual; an absolutist view of the rights of the individual could result in hindering scientific progress and subsequently, the common good.

As regards human experimentation, this situation fosters confusion between the interest of the patient, social utility and well-being through science. It also supports two types of simplistic approaches to questions: scientism and the rational calculation of usefulness. In response, there is a need for vigilance, ethically and legally, so as to avoid inconsistency between the idealistic invocation of principles and pragmatism which, when it becomes cynical, can lead to mercantilism. This is why it is important to question the normative framework of experimentation which gradually came into being during the 20th century, taking care to ensure that the prevailing cultural context does not affect the interpretation of the principles it sets out.

[2] Cf. in this respect: KENIS, Y., "Expérimentation, recherche, soins. L'expérience d'un cancerologue", in *Le devoir d'experimenter*, texts compiled by J.-N. Missa, coll. Sciences, éthiques, sociétés, Brussels, De Boeck University, 1996. p. 80-84.

4. PROBLEMS

The basic principles on which all human experimentation is based – as set out in the attached opinion, that is the principles of relevance, scientific rigour, 'no harm', autonomy and justice – raise a certain number of questions.

a. A *QUESTION OF METHODOLOGY*

Some members of the Advisory Committee believe it is essential not to look at questions raised by human experimentation from a normative point of view (solely in the light of the principles mentioned above), but again to take as a basis the description of situations that could lead everyone to question again the limits of the principles on which their ethical judgements are based. What should we so, for example when faced with patients, such as certain AIDS sufferers, who want to take part in an experiment despite the risks of which they have been informed? This situation leads to reconsideration of the link to be established between autonomy, vulnerability and acceptable risk-benefit ratio.

b. EXAMINING ETHICAL REQUIREMENTS - METHODOLOGY

Most texts on medical ethics and deontology put forward a series of principles which are based on different ethical outlooks, without suggesting a link between them. This situation may lead to excesses when one of these principles is considered to be the sole determinant, or when the ethical interpretation of the basis for this principle leads to a distorted interpretation of others. To overcome this difficulty, it would be advisable to suggest a methodology like that now put forward by certain texts[3], and accompany it with this rule: any condition not met releases the ethics committee from having to examine the following conditions; only protocols for which all the conditions examined, in order, have been given a positive assessment can be granted a favourable opinion.

c. THE LINK BETWEEN AUTONOMY AND VULNERABILITY

In addition to the principle of autonomy, it is also important to take account of a principle of vulnerability which not only expresses the condition of all individuals, but also requires particular attention when the experimentation concerns those who are weaker, such as those who are ill, children, the mentally disabled, the elderly, people in institutions or suffering from neuralgic disorders. So when an experiment involves those who are ill, the basic question becomes that of the link to be established between the risk accepted by the patient (autonomy) and the benefits the latter expects. The link between autonomy and vulnerability is particularly acute when experimentation is suggested as the last chance of a cure for a patient who is often distressed.

d. PARTNERSHIP

Rather than seeing consent as authorisation given by a patient or a subject to carry out an experiment on him as a procedure that aims to find out whether this patient or this subject illustrates the relevance of an assumption, would it not be better to see consent and

[3] Cf. in particular: CIOMS, *International Ethical Guidelines for Biomedical Research Involving Human Subjects, 1993, Guideline 14, Commentary, p. 38-39.*

experimentation rather as a partnership? In fact, the relationship between the doctor and the patient must be seen in terms of evolutive agreement that is constantly renegotiated. Actually obtaining informed consent implies abandoning medical paternalism. The doctor cannot decide alone what is good for the patient. He must take the time to correctly inform his partner-patient. The individual taking part freely in research is not an object being manipulated to achieve ends that have nothing to do with him. Ideally, he is an individual who is cooperating, to a limited but effective extent, on improving medical therapeutics and refining scientific knowledge of the human being. Would it not, therefore, be advisable to start from a position of uncertainty common to the patient and the observer?

e. CONSENT

Without calling into question the compulsory nature of free and informed consent, it should be pointed out that a careful analysis of international medical ethics and of Belgian deontology and law indicates that these normative sets all contain provisions that indicate a tendency to protect individuals, irrespective of any wish they may express. While consent must not be regarded as sacred, considered to be the sole expression of an individual's autonomy – which itself is wrongly identified with the dignity of human beings – it nevertheless plays a central role in a view that enhances the value of partnership. It is, however, important to stress that irrespective of the situation as regards standards, ethics committees remain vigilant regarding related questions.

f. INSURANCE

Whatever the causes and provided it relates to the experiment, any harm suffered by trial subjects, patients or healthy volunteers must be covered by insurance.
According to Article 6.3 i) of European Directive 2001/20 EC of 4 April 2001 (O.J. 1 May 2001), ethics committees must ensure that the experimentation is covered by insurance and check the clauses of this insurance.

g. SHOULD ALL EXPERIMENTATION PROTOCOLS BE SUBMITTED FOR ASSESSMENT BY AN ETHICS COMMITTEE?

The main aim of the rule underlying this question is to provide protection for those involved. However, this objective cannot be achieved. In fact, the cumbersome nature of the administrative procedure can lead to the planned medical activity being considered a therapeutic innovation rather than an experiment. Moreover, while the problem that the submission of experimentation protocols to the ethics committee is intended to resolve is that of the risks involved, there are many risk situations which are not collectively assessed if the doctors confine themselves to formal compliance with the requirements. This demonstrates the benefit of increasing awareness of ethics: it enables a more qualified assessment of the stakes for the various parties involved. It should also make it possible to avoid the situation in which always striving to protect people better, the regulations become ever more extensive, so that they weigh increasingly heavily and consequently give rise to strategies designed to avoid them.
Some people respond that everything that does not strictly benefit the patient must be assessed. But the concept of 'benefit' is not necessarily clear. This is why the question resurfaces, involving innovation on the one hand and experimentation on the other.

All experimentation requests must be the subject of an experimentation protocol, even if some investigators may be tempted, to avoid 'administrative red tape', to describe the

experiment as therapeutic innovation. The question of whether a plan for a multi-centre study that has already been approved by one ethics committee should be submitted for the assessment of another yields a positive response as the local experimentation conditions are not necessarily identical in each institution.

Another approach would be to rethink the demarcation between research through experimentation and experimental care, first taking into consideration the risks. This would mean it would not be necessary to submit certain experiments to assessment by committees, while henceforth some innovations should be so submitted, whereas until now they have escaped because they are assimilated to care. From this point of view, it would however be advisable to monitor compliance with the information and consent requirements.

D. THE CURRENT NORMATIVE FRAMEWORK

The legitimacy of experimentation activities is not provided for in **Royal Decree No 78 of 10 November 1967** on the exercising of the art of curing, nursing, paramedical professions and medical commissions (*Moniteur belge* of 14 November 1967), but these activities are expressly required elsewhere (**act of 25 March 1964** on medicinal products (*Moniteur belge* of 17 April 1964), **Royal Decree of 3 July 1969** on the registration of medicinal products (*Moniteur belge* of 10 July 1969)).

Furthermore, it should be noted that the European Directive on the registration of medicinal products **(Commission Directive 91/507/EEC of 19 July 1991***)* led to the integration into Belgian law of the concept of 'good clinical practice' (G.C.P.), including reference to the World Medical Association Declaration of Helsinki (**Royal Decree of 22 September 1992** amending the Royal Decree of 16 September 1985 on the standards and protocols applicable to trials on medicinal products for human use (*Moniteur belge* of 5 December 1992)). Finally, the **Medical Deontology Code** of the National Council of the Order of Doctors of **1 March 1993**, imposes on doctors deontological principles and recourse to the opinion of an independent ethics committee.

Article 70 *ter* of the act on les hospitals, included in this act by Article 194 of the act of 25 January 1999 (*Moniteur belge* of 6 February 1999) now established a legal basis for local committees by stating that "all hospitals must have a local ethics committee" and determining their missions; according to an annulment decree from the Court of Arbitration of 31 October 2000, these are as follows:

"1° a mission to provide support and advice concerning the ethical aspects of practical hospital care;
2° […];
3° an advisory function relating to all human experimentation protocols and human reproductive material".

These standards may, admittedly be considered inadequate. In practice, they are supplemented by the provisions of 'good clinical practice', the Declaration of Helsinki and the deontological rules.

Moreover, human experimentation is dealt with by the C**ouncil of Europe Convention on Human Rights and Biomedicine**, Oviedo, **4 April 1997.**

It is also worth noting in this context the **European Directive 2001/20/EC of 4 April 2001** on the approximation of the laws, regulations and administrative provisions of the Member

States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (O.J. 1 May 2001).

E. ETHICS COMMITTEES

The ethics committee procedure has one characteristic whose importance must be stressed. In fact, they are based on a collegial and pluri-disciplinary approach and they lie between the investigator and the trial subject, unlike the singular colloquium between the doctor and his patient, as their mission is to assess research protocol with regard to bioethical standards. They have the task of monitoring the application of the five principles set out in C.4 above and of discussing the problems that arise in each particular case. Fulfilling this task presupposes, in any case, that all ethics committees refer to the same assessment criteria for protocols and that the ethics committee members are informed of the methodology of clinical trials. Some members believe, moreover, that familiarisation with the rudiments of the various disciplines underlying bioethics is desirable. As well as medical and biological information, provision should also be made for an initiation into law and medical ethics.

1. COMPOSITION

The ethics committee must be composed of a reasonable number of members who together have the qualifications and the experience required to be able to judge and assess the scientific, medical, ethical and legal aspects of a research protocol involving human experimentation.

2. INDEPENDENCE

The ethics committee and each of its members must be able to carry out their mission successfully in total independence, whether this be in respect of the sponsor of the research, the researcher or the research institute, for example.
The procedure for appointment members must guarantee this independence**.**
In order that this ethics committee can fulfil its missions successfully as it should, its functioning must be funded in a manner that guarantees its independence in respect of the sponsor, the research institute and the researcher. The ethics committee must, moreover, render account of the use made of these financial resources.
The Advisory Committee believes that ethics committees set up within the pharmaceutical industry would not fulfil the independence criteria set by both medical deontology and legal requirements.

3. LIABILITY AND INSURANCE

The Advisory Committee believes that by giving its opinion on the ethical nature of an experimentation protocol, as on the other mission entrusted to it by Article 70 *ter* of the act of 7 August 1987 on hospitals, an ethics committee does not incur liability either on its own account or as regards its members because its opinion is neither a directive nor an authorisation and moreover, it is not carrying out the experimentation itself. Nevertheless, the Advisory Committee recommends that the hospital should take out adequate insurance to cover the members of the ethics committee for the consequences of any lawsuits.

4. OPTIONS TO BE TAKEN

a. NEED FOR AN ADVISORY OR A BINDING OPINION?

The principle whereby a research protocol should be given a positive opinion from an ethics committee, the monitoring framework (assessment criteria) and the assessment structure (missions and composition) are taken from various international documents:

- ICH guidelines,
- Directive 2001/20/EC of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (O.J. 1 May 2001),
- the Council of Europe Convention on Human Rights and Biomedicine, Oviedo, 4 April 1997.

Nevertheless, some members criticise this requirement for a mandatory positive opinion and put forward arguments in favour of a non-binding opinion, as currently required by Belgian legislation[4].

b. PROFESSIONALISATION OF ETHICS COMMITTEES?

Some members are concerned about the professionalisation of local ethics committees, which would entail the risk of a loss of perception of the reality on the ground. On the other hand, promoting the competence of the committee members is desirable.

[4] See opinion, C.1.

c. RESTRUCTURING ETHICS COMMITTEES TO FORM LOCAL COMMITTEES AND 'REGIONAL' COMMITTEES?

Some members of the Advisory Committee recommend introducing 'regional' committees alongside local ethics committees.
These 'regional' committees would have the exclusive task of assessing research protocols, in order to enable a certain level of professionalisation by combining the available resources and skills. With this system, the local committees' mission would simply be to check the feasibility of the planned research in the local context, and the 'regional' committees would be set up either by the local authority or on a voluntary basis in line with geographic or ideological criteria.

For other members of the Advisory Committee, creating a new structure like this is not only superfluous, but also inadvisable.
Superfluous, because Article 7 of Directive 2001/20/EC stipulates, in the event of multi-centre studies, that there shall be a procedure for the adoption of a single opinion per country. The other committees can limit the examination to ensuring that local conditions fulfil the requirements of the research. The ethics committee of a university hospital, for instance, could therefore give this sole opinion (moreover, this would virtually always be where the national coordinator of a study like this would be), without the need to create another structure. Moreover, the creation of a second structure would present two risks. First of all, distancing the ethical assessment structure from the situation on the ground will inevitably weaken the ethical debate in terms of proximity and favour the role of the bureaucratic control of ethics committees (assessment 'on paper') to the detriment of their educational and interactive role with the investigators within institutions; in addition, their role as regards the ethical aspects of hospital procedures will be weakened as their legal missions cover the same procedure, based on the same principles and often involve the same people. Finally, the creation of a second structure would lead to a haemorrhaging of competent people and financial resources to the new structures whereas these human and material resources are already limited and are better concentrated on existing ethics committees. These fulfil a substantial role that must be developed and supported financially, which is not always the case today. For these reasons of rationality and priority as regards objectives, it is essential to maintain the current structure while defining certain aspects more precisely: real means (secretariat, staff) must be allocated to existing ethics committees and a training programme must be gradually developed.

As regards research that is not carried out in a hospital (for example research carried out by general practitioners) or research that is undertaken in an institution which does not have its own ethics committee (retirement homes, rest homes and care centres, etc.), the question is which ethics committee the researcher should submit his protocol to. Four possibilities can be considered:

- firstly, the researcher can consult the ethics committee of his choice. Some members consider that this solution discriminates with respect to researchers linked to an institution that has an ethics committee, who obviously do not have this choice.
- a second possibility is to ask the researcher to contact a 'regional' committee set up for this purpose, with the risk that such committees only assess a small number of protocols and cannot therefore acquire a great deal of experience.
- a third possibility is to invite the researcher to submit his protocol to the ethics committee of one of the faculties of medicine or a university hospital, or if appropriate an inter-university ethics committee.

- a fourth possibility consists of asking the researcher to submit his protocol to an ethics committee set up, following the example of the *Vlaams Huisartsen Instituut*, within a professional group.

Local ethics committees would continue to exercise their function of support and advice concerning the ethical aspects of practical hospital care.

d. AN APPEAL STRUCTURE

Some members of the Advisory Committee feel that when an ethics committee issues a negative opinion on a research protocol, provision must be made for the possibility of appealing. Nevertheless, it is important not to lose sight of the fact that if the appeal decision were to overturn the negative opinion, the researcher would in practice come up against resistance from the institution concerned, which could not be forced to permit this research to take place on its premises.
Other members think it is pointless to make provision for an appeal if, irrespective of the opinion and even if it is negative, it is not binding; in this case, indeed, either the hospital will not agree to implement a project that has been rejected by its own ethics committee or the investigators and the hospital will take their responsibilities in fully knowledge of the facts, the researcher having to appear before the committee if, despite the negative opinion, he would still like to carry out the research project. In any case, it seems essential to all members of the Advisory Committee for the investigator to be heard in a debate between both parties before the ethics committee issues a negative opinion.

e. FORUM SHOPPING

In order to avoid forum shopping, some members propose that a given research protocol can only be submitted to one ethics committee, the choice of which may or may not be left to the discretion of a the researcher; moreover, he should only be able to consult an approved ethics committee, which raises the question of the legitimacy of non-hospital ethics committees: a certain number of them should be recognised owing to their experience and their independence, particularly as regards sponsors. The solution of ethics committees linked to medicine faculties or a university hospital is an interesting avenue in this respect.

Other members do not object to investigators requesting multiple opinions, provided that they are obliged to include the opinion or opinions already obtained.

F. ETHICAL ASSESSMENT OF AN EXPERIMENTAL PROTOCOL – PROCEDURES

1. THE ETHICAL LEGITIMACY OF THE AIM

This first principle which is essential for the legitimacy of any act of human experimentation in actual fact combines three parameters:

a. the scientific interest of the project
b. drawing up an adequate protocol
c. the existence of prerequisites.

a. THE SCIENTIFIC INTEREST OF THE PROJECT

Submitting a human being to an experiment of any kind whatsoever can only be rendered legitimate by the importance of the information which this may be expected to yield in the field of health in the broad sense of the term, including the understanding of physiology and physiopathology. It is therefore essential to be able to justify the way in which the planned experiment will contribute to an improved knowledge of humans by means of a new contribution at one level or another that is worth achieving. There is indisputably a link between the importance of this interest and the risks examined later on, but the scientific interest criterion exists absolutely in spite of everything: no scientific interest, no ethical legitimacy. This applies, for instance, for repetitive studies without any scientific interest and raises the question of the legitimacy of multiplying essentially similar medicinal products, which implies bioequivalent studies of doubtful interest.

b. DRAWING UP AN ADEQUATE PROTOCOL

If the project is of scientific interest, does the protocol put forward (that is the document describing the methodology that is to be used) answer the question asked? This is a particularly important requirement which relates to the very principle of economy: when embarking on an experiment, it is essential to have the means to achieve the aim sought. Otherwise, people are pointlessly subjected to a protocol which would not lead to rigorous and valid conclusions: a situation like this leads not only to wasting human and material resources, but can also cause confusion in a field of knowledge and (rightly) discredit human experimentation itself. Another aspect that should give rise to critical examination of the protocol concerns alternative methods: could the protocol be implemented less expensively (principle of economy) or even on an animal model or an ‘in vitro’ model? The requirement for an adequate protocol comprises multiple facets: drawing up the experiment, validity of the measuring instruments and statistical methods, size of the sample tested. But this requirement also relates to the practical aspects of implementing the protocol examined in point 3.

c. THE EXISTENCE OF PREREQUISITES

This requirement recalls that, as a matter of principle itself, rigorous scientific procedure is based on prior knowledge. While this is true for all scientific experimentation, it is particularly important in human experimentation: have all the existing data relevant for the protocol in question been examined? Do these prior data give legitimacy to the project? Are the prior data (especially the data gathered during animal experiments and

previous experiments on human subjects) sufficient to move on to the planned stage in the study?

2. PROPORTIONALITY OF RESOURCES

The concept of the proportionality of resources is a conventional if complex concept in medicine: it refers to the fact that all acts (a fortiori all acts of experimentation, however harmless they may appear) entail a risk. Does the anticipated benefit justify this risk? But also: is there an alternative, less risky method of answering the question asked? (We are thinking here, for instance, of the new possibilities of experimentation on isolated cells, even though at some point human experimentation becomes essential).

With experimentation carried out for therapeutic purposes, the anticipated direct benefit for the patient may make a high risk acceptable, whereas in the case of purely cognitive experimentation, risk for the person taking part in the experimentation must be slight. On the other hand, the risk assessment must cover the entire experimental procedure (and therefore include, for example, the examinations necessary to assess a new medicinal product), the procedures for the inclusion and exclusion of trial subjects, and the procedures for withdrawing from the experiment and those that apply in circumstances requiring a halt to the experiment.

The concept of risk, too, is complex: the risk for the individual is expressed in terms of physical and psychological risks, but also in social and economic terms. But other aspects of the risk also have to be taken into account, such as its seriousness, the probability that it will arise, its reversibility and the possibility that the investigator can overcome it. Overall, this is a difficult assessment, even if serious accidents appear to be exceptional, in any case in the field of trials of new medicinal products.

3. QUALIFICATION OF THE INVESTIGATORS AND EXPERIMENTATION ENVIRONMENT

The need for an adequate protocol and the assessment of the risk make it necessary to consider the quality of the investigator (is he the most competent person to carry out the planned experiment?) and the resources available, not only to carry out the experiment with optimal efficacy but also to respond to any unwanted effect.
The experiment must be undertaken by qualified and competent people in a suitable environment. This requirement involves clearly identifying the investigators and justifies the need for the dossier to be submitted to the ethics committee by the principal investigator (and not the promoter). It also involves having access to the curriculum vitae of the investigators, and the need for the ethics committee to be familiar with the environment in which the experiment is to take place.

4. FREE AND INFORMED CONSENT

The process of obtaining free and informed consent is a crucial stage in the ethical legitimacy of a research protocol, placed at the head of the ethical requirements of biomedical research even by the Nuremberg Code of 19 July 1947.

a. PRIOR INFORMATION ESSENTIAL FOR INFORMED CONSENT

The consent must be informed, that is prior to giving consent, the individual must have been informed of the study and the methodology used, the length of study, the anticipated benefits, the constraints, the foreseeable risks, the undertaking to ensure the confidentiality of the data, compensation, the right to withdraw from the study at any time and the possible communication of the results**.** It is crucial to clearly separate acts and examinations linked to the experiment from those that are part of the usual treatment of the patient, both on the information form and on the consent form. The main points of this information must be included on an information form drafted in comprehensible terms and as far as possible in the language of the patient and attached to the consent document so that there can be no challenge regarding the information which the patient (or the healthy volunteer) has received. A further oral explanation from the investigator is necessary in order to be adapted to the understanding of each individual and so that questions can be asked. The information document must expressly indicate which ethics committee or committees has (have) given an opinion, and the content of this opinion**.**

b. OBTAINING CONSENT

The French act of 20 December 1988 on the protection of individual who take part in biomedical research (the Huriet act) stresses the fact that, thanks to their consent, the individuals included in a research project become partners who can collaborate actively with the investigator, emphasising the importance of this informed consent. This must be personal, prior and preferably laid down in writing. It must be free (that is exempt of any pressure, including moral or financial pressure). The aspect of compensation to cover the costs incurred by the patient or any other indirect advantage (free medical products for some trial subjects, for example) is particularly tricky.
The principle of compensation is that it can only offset any inconvenience suffered (costs incurred, lack of work, etc.) and cannot become remuneration which may constitute an incentive. The direct advantage may become an incentive, for example, for patients without social security.
It must be possible to withdraw consent at any time without giving a reason and without any consequences, which involves taking very specific precautions when the consent is obtained by the general practitioner, which is usually the case with human experimentation involving a patient.

The validity of this information and this consent is subject to the same type of discussion as information and consent in the context of medical acts. As for such acts, it must be fair and complete without presenting all the eventualities that are theoretically possible in full, which would become a source of anxiety. Finally, as regards the condition of the patient, it must respect his wish to know the seriousness of his condition or not. It is generally considered necessary to pass on "all information that a reasonable person would deem important to take the decision to consent". This information must include the details relating to liability and insurance in the event of an accident, the limits of the confidentiality of the data obtained and the opinion and comments from the ethics

committee that examined the protocol. This information must also be updated as the experiment progresses when relevant new information becomes available.

5. CONCLUSION

In addition to these general rules, there are also special rules that are not part of this opinion for vulnerable groups and special situations such as:

- healthy volunteers;
- individuals who are legally or de facto incapable (psychiatric patients, unconscious patients, underage patients);
- the protocols of behavioural studies where obtaining consent prevents the experiment from being carried out at all;

- socially vulnerable groups: separate cultural communities, prisoners, persons who are be likely to be forced (such as medical students), persons in need;
- pregnant or breastfeeding women;
- in vitro human embryos;
- experiments on cadavers;
- experiments on organs, tissue or tumours removed from patients;
- experiments on the products of spontaneous or induced abortions.

It appears that a growing number of firms are asking to keep samples with a view to carrying out subsequent genetic analyses. A procedure like this which may involve research carried out unbeknown to the patient poses particular problems and will be the subject of a separate opinion.

The aspects of data confidentiality are in principle governed by the legislation on the protection of privacy (act of 8 December 1992 on the protection of privacy with regard to the processing of personal data (*Moniteur belge* of 18 March 1993)) and the directives of the National Council of the Order of Doctors concerning access to human experimentation dossiers (opinions of 22 August 1992, 17 February 1996, 13 December 1997, 19 September 1998, 24 April 1999, 15 January 2000 and 19 February 2000).

Finally, for some members, ethics committees should follow up the protocol (information on progress with the experiment, interim results, unwanted side effects), which for them constitutes an activity that is as yet unfamiliar. Other members, however, believe that this mission should not be entrusted to them.

This introductory report for the opinion was prepared in select committee 97/8 consisting of*:

Joint chairpersons	Joint reporters	Members	Member of the Bureau
M. Bogaert Y. Galloy	M.L. Delfosse (2000) E. Guldix	M. Abramowicz ('96-'99) M. Baum P. Devroey X. Dijon (demission '98) I. Liebaers ('96-'99) J.N. Missa (2000) H. Nijs G. Sokal ('96-'99) M. Somville ('96-'99) J. Stiennon (demission '99) F. Van Neste	Y. Englert

Member of the secretariat: E. Morbé

Permanent experts:

- Ms M.L. Delfosse (1996-1999), philosopher, Facultes universitaires Notre-Dame de la Paix-Faculte de droit, and CIDES, Namur.
- Ms I. Liebaers (2000), lecturer, Centrum Medische Genetica, AZ-VUB, Brussels.
- Mr J.N. Missa (1996-1999), philosopher, CRIB, director of the Institut de Philosophie at the ULB, Brussels.

The working documents of select committee 97/8 – request for opinion, personal contributions from members, minutes of the reunions, documents consulted – are stored as Annexes 97/8 at the Committee's documentation centre, where they may be consulted and copied.

* Some members took part in the work of the select committee during the Committee's two terms of office (1996-1999 and 2000). The length of the term is indicated next to the names of the members who took part in the work of the committee during a single term of office.