Opinion n° 79

Transposition into French law of the European Directive relating to clinical trials on medicinal products: a new ethical framework for human research

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Introduction

On April 2, 2003, the *Direction Générale de la Santé* referred to CCNE regarding the ethical implications of transposing into French law the new European directive 2001/20/CE obligating member States to harmonise their legal, regulatory, and administrative provisions for the conduct of clinical trials on medicinal products for human use[1]. Specifically, this directive, differs from the provisions in the Huriet-Sérusclat Act of December 20, 1988 in that it:

- forgoes the concept of research "with" or "without" direct individual benefit (DIB), and introduces the notion of evaluating the "benefit/risk" balance.
- extends the responsibilities of the CCPPRBs (*Comités Consultatifs de Protection des Personnes se prêtant à la Recherche Biomédicale*) (committees for the protection of persons participating in biomedical research programs) which would become "Committees for the Protection of Persons involved in Research" (CPPR). The extension is needed because the concept of "research without DIB" is eliminated, and the "prior authorisation of research sites" for healthy volunteers is almost completely removed.
- makes it mandatory to keep a national register of subjects involved in research only for medicinal products within the competence of AFSSAPS (*Agence Française de Sécurité Sanitaire des Produits de Santé*) (French Health Products Safety Agency) and for healthy volunteers or patients for whom the expected benefits are in no way related to their pathological condition.
- provides that, for persons who are incapable of giving consent to research, a legal representative will be consulted.

Initially, the Huriet-Sérusclat Act mainly centered on research concerning medicinal products. Although the law does not actually establish any *a priori* distinction between individuals participating in research, it does introduce a notional difference (with or without "direct individual benefit") classifying participants into two sub-groups (research with direct individual benefit which does not concern healthy volunteers).

It was based on the principle that research could only be conducted with consenting individuals. Otherwise, in cases of incapacity, research could only be conducted in the interest of the person concerned. Taking into account the benefit/risk balance, that the European Directive requires, is a pertinent semantic development in both scientific

[1] Directive 2001/20/EC of the European Parliament and of the Council 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. Official Journal of the European Communities L-121 dated 1-5-2001, pages 34-44. Available at: http://europa.eu.int/eur-lex/en/archive/2001/l_12120010501en.html

and ethical terms, but as a result, the consequences for persons who are incapable of giving consent must be examined.

I. Changing the notion of "DIB" into "benefit/risk" balance

I.1. The limits of classical terminology

The benefit-risk ratio qualifies the sum of expected advantages weighed against possible drawbacks. Withdrawing the usual concept of "direct individual benefit" (DIB) and replacing it with the "benefit/risk" reference, is a step in the direction of more principled research. CCNE had previously emphasised[2] the need to establish a clear distinction between two types of research, with or without DIB, although this distinction was not taken up in the 2000 version of the Helsinki[3] Declaration. Specifically, the CCNE Opinion stated:

"This qualification would be entirely reassuring if the Huriet law made a clear distinction between "research with direct individual benefit" and "research without individual benefit". The dividing line has been a source of some perplexity ever since the law was voted, *inter alia* in the deliberations of the CCPPRBs. It has been disputed internationally. This is not the place to enter into a discussion on the subject, except to say that in order to make matters clearer to those whose consent to research is asked for, and for discussions in CCPPRBs, a research protocol declared as being "with BID (*bénéfice individuel direct* - direct individual benefit)" should explicitly list the "direct benefits" that the participating 'beneficiary' can expect to gain."

In any event, because of their severity, the constraints imposed on research "without DIB" (originally aimed at phase I or phase II therapeutic trials on healthy volunteers) turned out to be "ill-suited to a great many situations, such as research on blood samples during routine therapy"[4]. In some cases, the result was that possibly fictitious DIBs were claimed. Furthermore, the creation of specific sites for this type of research was such a complicated matter that clinicians stated that the research did indeed provide DIB for the patient or subject of research, even when that benefit was extremely trivial, or even hypothetical. The absence of DIB also rendered certain studies almost impossible although they were in fact essential, such as purely cognitive or physiopathological studies, or those required in an emergency.

Furthermore, the historic distinction between research 'with' or 'without' DIB, the original intention of which was logical, led to blurring the boundaries between research and care, whereas it is important to maintain a clear separation between the

[2] CCNE. Report and Recommendations n° 58, June 12 1998. Informed consent of and information to persons accepting care or research procedures Available at : http://www.ccne-ethique.fr

[3] Declaration of Helsinki by the World Medical Association, October 2000. Available at : http://www.wma.net
The initial 1964 version of the Declaration of Helsinki proposed : « 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.

[4] Lemaire F., « revision of the law dated December 20 1988 : common platform of proposals from scientific associations, organisations and patients associations ». Réanimation, 2001; 10: 435-8; Ed. scientifiques et médicales Elsevier.

two activities, even if in practice there is a growing tendency for them to merge. This was precisely the major contribution of the Huriet Act, i.e. the creation of a specific legal framework which gave autonomy to research within the general field of medical practices. Care is a therapeutic activity, which is addressed to the subjectivity of a singular *person*, whereas research works in the direction of the objectivity of a biological *individual*. The former integrates the personalised audition of a subject, whereas the latter is an epistemological pursuit to reveal the impersonal laws of life. Research is the process of verification of a hypothesis with the aim of endorsing its conclusions in the form of generally applicable knowledge. This objectisation of the patient in experimental research is a methodological requisite. By eliminating all that is purely subjective and contingent (impressions, aspirations, and emotions) the study of disease can advance[5].

It is however this process of turning a patient into an object or "a sample of a disease" which makes the duty of personal protection so crucial. The notion which prevailed until the present time – that of "direct individual benefit" – becomes incomprehensible unless one remembers that its aim was to protect a person. Its aim was to lessen existing tension between individual health and public health, by subordinating research to immediate personal care . The role of a physician is to help a sufferer, but it is acceptable for this objective to coexist with the none less laudable aim of furthering the advance of medical science for the benefit of the community[6].

This subordination of the collective benefits of research to the individual dimension of care was flawed because it rendered certain forms of investigation almost unintelligible. The opinion that "patients treated in the framework of a therapeutic trial achieve better results than those obtained by routine treatment"[7], is not devoid of truth, but this should not blind us to the clashes of principles that arise for example in research involving placebos. In fact, it is research with DIB that potentially generates the most serious risks. The most concrete example of this is research on mortality differentials between treated groups and control groups in various trials.

To further illustrate the point, several clinical situations demonstrate the ambiguous nature of the DIB concept. Molecules prolonging the life of terminal patients, seem at first sight to be doing them good. However, it is not unreasonable to wonder whether benefit can be expressed purely in terms of the number of years or months of life that are gained. Hence, the development of a new molecule that makes it possible to extend the life of a patient suffering from an incurable disease is progress that in certain cases may not coincide with an improvement in the quality of life of that patient. If, for research to be ethically acceptable, it was necessary to be sure from the outset that it was going to lead to improvement in the quality of life of patients, many investigations might well be suspended or prohibited. Research frequently leads to

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5 Bachelard G., *La Formation de l'esprit scientifique*, Vrin, Paris, 1938, Chap. XII, p. 239: *« Il faut donc accepter une véritable rupture entre la connaissance sensible et la connaissance scientifique »* (A real break between sensitive knowledge and scientific knowledge must be accepted). The author also makes some suggestive remarks concerning a « constant effort of desubjectisation » in order to define scientific progress (Ibid. p. 249).

6 The aim of research, as the Huriet Act stated in article L. 1122, « is to extend scientific knowledge of human beings and the means of improving their circumstances ».

7Hoerni B., *L'autonomie en médecine. Nouvelles relations entre les personnes malades et les personnes soignantes*. (Medical autonomy. New relationship between the sick and the carers). Bibliothèque scientifique Payot, ed. Payot, Paris, 1991, p.118.

discomfort, which patients would not have endured had they been in a strictly therapeutic environment (repeated blood or urine sampling, for instance). However, the very notion of quality of life is so subjective that it cannot become a valid parameter for ethical objectivity.

The effect of the indeterminate nature of the notion of "direct individual benefit" has been to detract from the coherence of the 1988 provisions as regards the protection of persons. The result has been to expose to the vagaries of research subjects (incompetent minors, protected adults) in the name of uncertain "direct benefit for their health", whereas the stated purpose was to protect individuals from research to which they had not given consent. Retrospectively, it would appear that the notion of DIB may have allowed certain investigators to elude the rule of prior consent so as not to exclude from research persons for whom further scientific insight into their pathology was wanted. In fact, although securing consent was originally designed to protect certain categories of people, it turned out to be in some cases the most subtle method of bypassing the actual condition of that protection.

I.2. Adjusting the European Directive to the practicalities of biomedical research.

The modifications to the terminology, which the Directive requires, help to clarify the meaning of investigational procedures. However, special attention should be paid to themes which it does not explicit and which require the legislator's specific notice.

An excessively punctilious implementation of the benefit/risk balance could lead to *de facto* prohibition of pure cognitive research, and of phase I trials for sick volunteers for whom the risk, more often than not, outweighs the expected benefit. It would seem that use of the notion of benefit should be sufficiently flexible to allow biomedical research to alternate between individual and collective perspectives, and recognise as ethically fully allowable in research[8], the existence of collective interests, and not solely individual interests. As has been justifiably commented: "there is a chain of solidarity between successive cohorts of patients. Those of today benefit from the knowledge acquired by observation of previous patients. Therefore, it is neither monstrous nor even immoral to expose them to minor discomfort which could provide new insights that will be useful to improve the treatment of future patients. For that matter, patients frequently express the hope that they will be contributing to progress".[9] It is not unethical to practice investigation with a collective perspective, but it is contrary to ethics to lose sight of the personal interests of the patient who then becomes a mere object of research. In this connection, it must be said, quoting CCNE's Opinion 58, that "Although contributing to research can be seen as a duty for the sake of solidarity, French law does not make solidarity compulsory ».

8 On the subject of phase I trials, Opinion 73 points out that : *« As a result, information given to patients regarding the uncertainty of any benefit, the possibility of adverse effects, and ensuing risks, often leads to some confusion. More or less consciously, there is a tendency to minimise problems, so that no truly informed consent is achieved ».*Available at: http://www.ccne-ethique.fr. On this point, as a comment concerning the drafting of the Directive (article 3-2.a) : "*the foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients»* could be replaced by the formulation and/or other present and future patients.

9 *Ibid*., p. 116

These ethical considerations are related to CCNE's recent discussion on the ethical implications of phase I trials in cancerology[10], and on the difficulty of providing information and securing informed consent in such cases.

Similarly, research on healthy volunteers (for whom there is no possible 'benefit', whereas 'risk' can never be discounted altogether) also has specific characteristics, so that the particular protective measures now enshrined in legislation should not be dropped (e.g. a special kind of insurance system, possible compensation, and recording such research without DIB in a trials register).

These two points being emphasised, the new recommended denomination – evaluation of the benefit/risk balance – appears to be more pertinent than the previous classification of research as a function of DIB, where the « risk » element was implicit but not explicit.

I.3. Identifying the types of risk as the starting point for the essential issue of information

I.3.1. Medicine and the principle of precaution

The risk factor in medicine is increasing. Can the principle of precaution apply to medicine? Defined as the probability that a medical act leads to complications and injury, it requires a "contractual" discussion of the advantages and drawbacks of the various therapeutic options. This discussion is not solely applicable to therapeutic trials. Points arising could be patients' desire to participate in their treatment when objective data on the efficacy of treatment is not available, situations where there is a true choice between invasive or non-invasive treatment, or, by treatment, transforming quality of life into life expectancy.

Risk analysis entails recognition of the physical, psychological, social or economic implications which are to be the object of prospective, explicit, and objective information. This desire to anticipate is no novelty as such. Risk investigation is consubstantial with medical activity. A practitioner's individual conduct is always guided by the Hippocratic principle of *« primum non nocere »,* with the clearly expressed obligation to seek to prevent known or obvious risks, when diagnosing[11], prescribing, and carrying out medical acts[12], although risks – known or unknown, or unforeseeable – may sometimes have to be taken, for instance in an emergency[13].

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[10] CCNE: Opinion N° 73 Phase 1 studies in cancerology. Available at : http://www.ccne-ethique.fr

[11] art. 33 of the *Code de Déontologie*: "*...by devoting the necessary time, by using to the greatest possible extent the most suitable scientific methods and if required, appropriate assistance* ». This article is complemented by the prevention of risk : *«in his investigations and interventions, the physician must refrain from putting the patient at any unwarranted risk »* (art. 40)

[12] art. 70 of the *Code de Déontologie*: A physician must not « *undertake or continue care, or prescribe in domains which are beyond his competence, experience, or the resources available to him* »

[13] art. 9 of the *Code de Déontologie*: "*Any physician in the presence of a patient or casualty in danger, or if he is informed that a patient or a casualty is in danger, must assist him or ensure that he is given the necessary care ».*

However, although risk has always been at the core of medical activity, contemporary medicine is unique in that its field of action has become the scene of technological developments which society is attempting to negotiate from a critical viewpoint, *via* a "principle of precaution". From the simple virtue that it used to be ("steps taken to avoid harm or attenuate its effects"), in the last few decades, precaution has progressively been elevated to the rank of a political and legal principle for the management of production tools through various national or international instruments. Among these writings, one can quote the Rio Declaration on Environment and Development published on June 13th, 1992, and ratified by France on June 20th, 1994:

"Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation".

The proposal to include the charter for the environment in the Constitution would move in the direction of turning it into a constitutional principle.

The initial purpose of such a principle was explicitly to regulate the industrial activities of those promoting new technologies from the point of view of their effects on the environment. However, since the environment is closely linked to the health of its citizens, the European Commission has accepted the idea that the European Union was entitled to include the health sector within its purview (February 2nd, 2000). As regards French legislation, although the first appearance of the principle of precaution was in the 1995 Barnier Act, it was through jurisprudence that it was first introduced into the public health sector[14]. Although healthcare innovation is regulated by the principle of precaution, biomedical research needs to address the issue of the status it should be granted in case of scientific uncertainty regarding the consequences of risks to the health of those participating in trials of medicinal products.

I.3.2. Precaution and Prevention

The first point to be made is that the Rio text quoted above (and this is also true of article L. 110-1 of the *Code de l'Environnement*) makes a close connection between precaution and prevention against hazardous materials and activities, which authorities are supposed to forbid the production of, instead of waiting until they reveal themselves as harmful retrospectively. However, although the principle of precaution presents itself as a form of prevention, **it does not follow that prevention is always simply an application of the principle of precaution.** Prevention, when it is guided by evidence and analysis of a specific risk, is a rational activity that aims to take steps appropriate to the nature and probability of the risk concerned. The principle of precaution, however, sets out to respond to uncertainty, by anticipation based on the hypothetical, the unverifiable, and the imponderable[15]. "Precaution relates to potential risks, and prevention to substantiated risks[16]". Let us also be clear that a "potential risk" is not a risk which is already latent, a kind of virtual danger which is waiting to reveal itself in the full light of day. A potential risk is not an "immature substantiated

[14] The subject at the time was suspending authorisation for cultivating genetically modified maize.
[15] B Glorion, Bull Acad Natle Méd 1998, 182: 1219-28
[16] Kourilsky P., Viney G., report to the Prime Minister, presented on 15-10-1999 http://adlp.free.fr/kourilsky.pdf

risk, awaiting fulfilment"[17]. Of course, it is always possible to state with hindsight that a substantiated risk already existed "potentially", and that therefore it could have been avoided by observing the principle of precaution. However, history teaches us that examples abound of risks thought to be "potential" at the time and later found to be non-existent. Think of all the so-called "potential risks" to health which the contemporaries of major innovations warned against, such as potential risks to health caused by speeds exceeding 20 Kms/hour, going through tunnels, or even underground drainage[18] systems.

The above examples demonstrate on the one hand, that counting on the principle of precaution is in itself risky (if only the risk of being mistaken in an evaluation of potential risk). Evaluation should therefore make it possible to identify among hypothetical risks those which are plausible and those which are more likely to be imaginary, and this requires a joint effort on the part of experts and professionals[19]. They also go to show that the natural tendency when anticipating is to plead in favour of abstention (not go faster than 20 Kms/hour, not have the train go through the tunnel, etc.). That is the reason why the principle of precaution is often seen as an obstacle to innovation and so vigorously disputed using that argument.

In its report "From the principle of precaution to the concept of anticipation" in February 2003, the *Académie Nationale de Médecine*, emphasised that "The attraction of the principle of precaution for public opinion is that it appears to be an instrument for warding off the threats of the future, when the dangers feared are still vague and imprecise" [20].

As it seeks to remedy the limitations of the scientific mode of action, the principle of precaution carries the risk of becoming a substitute for it. This contradiction raises the major issue of expertise and experts, as has been rightly emphasised. [21] [22]

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[17] Kourilsky P., *Du bon usage du principe de précaution,* Odile Jacob, Paris, 2002,, p. 43.
[18] For these examples, cf. Kourilsky P., *op. cit*., pp. 43-44.
[19] *Ibid*., p. 51.
[20] The *Académie Nationale de Médecine* expresses its comments as follows : « Therefore, scientific expertise must accompany the entire phase of preparation and implementation of the measures to be taken. But it should certainly not trespass into taking decisions. That is entirely a political matter ; that is the level where all the factors, social, economic, and political, can be taken into account, with the possible consequence that there can be deviation from the conclusions suggested by the expert opinions. The very normal possibility of such deviation is one of the reasons why the components of the expertise, and the elements of decision, must all be totally open to scrutiny ; this is one of the major contributions of the principle of precaution. In this way, ulterior and retrospective analysis will have a sound basis ».
« The principle of precaution which promises quasi absolute protection could pervert the practice of prevention, i.e. the management of known risks. In such a situation, a possible limit to precautionary measures is found acceptable because they would be disproportionate to the probability of risk, or because of their cost. By invoking the principle of precaution, that limit is obliterated ».
« Thus we note that the principle of precaution weighs excessively on political decision if it is taken up by the media. This could open the way to manipulation which would be difficult to keep in check. »
[21] M.-A. Hermitte, *La liberté de la recherche et ses limites*, (Freedom of research and its limitations) coll. Droit et Technologies, 2001
[22] C. Noiville, *le gouvernement des risques, (Governing risks)) coll. Les voies du Droit, PUF 2003*
[23] Ewald F., *Rapport rendu à la commission de rédaction de la Charte de l'environnement*. (Report to the drafting committee of the Charter for the Environment) .
(http://www.charte.environnement.gouv.fr/index)
[24] Jonas H., *Une éthique pour la nature* (Ethics for nature); Desclée de Brouwer, Paris, [1993], 2000, p. 73.

I.3.3. The principle of precaution: from theory to practice

To try and be clearer on this point, the substantive version and the procedural version of the principle of precaution will be dealt with separately[23].

In the "substantive" version, the principle of precaution prohibits the implementation of a project under study if, as a result of discussion by experts, an argument which demonstrates the *possibility* of risk cannot be countered by an argument to the contrary demonstrating that there is nothing to be afraid of. In that case, uncertainty plays in favour of abstention. This substantive version falls under Hans Jonas' philosophical theme: the "principle of responsibility". The general tenor of this concept is the "priority granted to bad prognosis over good prognosis". One of his formulations sums up the substantive version of the principle of precaution to the effect that *when there are two opposite prognoses as to the consequences of major technological revolutions, one favourable and one unfavourable, preference must be given to the unfavourable prognosis and forgo, or at least slow down, the process*[24]. It can be observed that the decision is dictated mechanically by a general directive. The principle of precaution gives it a specific content: abstention if there are potential risks. He gives to the question asked the "substance" of a general response (hence the name "substantive" version).

In its "procedural" version, the principle of precaution does not proscribe a risk bearing action; it calls for weighing the risks involved, it being clear that *the only choice we ever have, is choosing between various risks* (abstention itself is indirectly a source of risk: delaying progress, penalising innovation, etc.). It prescribes for instance that we ask what are the serious and irreversible risks associated with not implementing a certain technique (e.g.: what might we be deprived of by prohibiting GMOs?). Seen from this angle, the principle of precaution does not suspend action; it requires that action be taken according to other criteria than exhaustive and assured knowledge of the consequences of action. In the case of variant Creutzfeldt-Jakob disease, for instance, the principle of precaution does not forbid the import of meat as soon as there is some doubt concerning the production process. It is in the « substantive » version that uncertainty regarding the risk connected to contamination of the meat concerned is perceived as demanding the prohibition of imports. In its procedural interpretation, scientific uncertainty may lead to accepting importation but on condition that import control procedures are reinforced. This risky action is not a contradiction of experts' opinions since they recognise that they cannot quantify the risk by determining the probability of its appearance. The principle of precaution cannot be summed up as saying "when in doubt, abstain"; what is says is "when in doubt, evaluate the respective risks of action or inaction". It is not because knowledge about the future is uncertain that one should conclude that an action must not be allowed. To wait for unshakable convictions regarding the severity of a danger before taking any action can lead to disaster[25]. Scientific uncertainty has never dictated, and

[25] The principle of precaution, in real life, amounts to choosing, as best one can, among the various possibilities (innovation, statu quo, various different innovations…) the line of action which fits in as well as possible with the principle of precaution. Quite obviously, this does not lead systematically to the statu quo. To take a medical example, the principle of precaution is

must not dictate political decision, which must always have freedom of action as regards experts who can only formulate hypotheses.

This serves to clarify the « procedural » version of the principle of precaution. In this case, faced with the possibility of a potential risk, a procedure of deliberation is launched in order to evaluate the degree of plausibility of the risk. Decision stands alone; it is not linked to an *a priori* prescription, as is the case with a substantive reading of the principle:

« In this version, the principle of precaution appears to be a procedural (…) mode of decision, because it does not in any way presuppose the substantial decision that needs to be taken; it simply guarantees equitable conditions for the fullest possible exchange of views and information »[26].

As regards clinical trials on medicinal products, this Opinion pleads in favour of the procedural version of the principle of precaution, which is closer to general medical practice. Medically, the fact that an action carries a potential risk cannot be sufficient reason for abstaining from that action. In this case, "there is a certain degree of tolerance for the residual marginal risk because of expected therapeutic benefit, the evaluation of which is a basis for applying the principle of proportionality. It is obvious to all that an excessively security minded attitude could compromise therapeutic benefit"[27]. In order to avoid minor injury, the patient would frequently be exposed to life-threatening risk. For example, therapeutic toxicity is often the downside of the increased efficacy provided by a new medical technique. Because there are cases where hospital care makes a patient worse cannot lead us to the conclusion that a doctor must always observe the rule that doing his patient some good must be subordinated to doing him no harm. Giving this kind of systematic supremacy to the principle of not doing any harm would lead to paralysing any therapeutic intervention if it was predictable that it would have iatrogenic effects.

In medical practice, the *first* principle is to do no harm (anticipate the damaging effects of treatment) and the *second* to aim to do good, while being aware that the first objective generally takes the second along with it. When a patient is in a state of temporary coma with signs of awakening, for example, the medical staff treating him will attempt to do more and better than just doing him no harm. Although in such cases, decisions will have to be taken which should have been taken by the patient, and medical action will have to be taken without the patient's prior consent, the decision to save that patient with the least possible sequellae is based on the principle of benevolence and far removed from a principle of doing no harm which would only dictate that matters not be made worse. There is therefore a *primary* principle of doing no harm, but *primacy* of the principle of benevolence. A situation of uncertainty cannot ever justify abstaining from treatment as would entail the substantive version of the principle of precaution.

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quite frequently in favour of action : faced with the plausible risk of an epidemic of smallpox, for instance in a situation of biological warfare, vaccination clearly corresponds to maximum precaution, despite its intrinsic risks.

[26] Hunyadi M., "Pourquoi avons-nous besoin du raisonnement de précaution? » (Why do we need the rationale of precaution?), in *Esprit*, n° août-septembre 2003, page 148

[27] Kourilsky P., *op. cit*.,p. 31.

I.3.4. Precaution and information

As a result, when communicating information to a patient, serious and irreversible risks must be clearly stated to the participant, but possible risks do not demand any further precaution than being correctly evaluated. The important aspect is the requirement for transparency, not futile emphasis on uncertainty. The maximising procedure called for by the principle of precaution does not concern the information to be given to the patient; it is attached to the exploration of risk by investigators. Patients would have difficulty in understanding why they are being given descriptions of all the risks which came to the minds of the developers of the research protocol, including those which have not been verified. There again, the potential risk corresponds to a *theory* elaborated by the researchers, and in no way to a *danger* waiting to happen. There is therefore no need to include it in the information process.

This was the meaning given by CCNE in its Opinion n° 55 regarding information to be offered on the subject of blood-borne transmission of the Creutzfeldt-Jakob disease, as follows[28]:

> « Information on the potential risk of some therapies, when it is not based on scientifically confirmed facts, is not the same thing as information on the treatment itself.
>
> Once a risk is known and scientifically demonstrated, there is an obligation to inform the patient. If, however, the risk is virtual and theoretical, there is no ethical justification to giving information since it may be perceived as a vague unidentified threat which could lead to irrational behaviour, possibly dangerous to both patient and society. »

The prospective discussion of risk is related to information to patients, which has recently been the subject of recommendations to practitioners, drafted by the *Agence Nationale d'Accréditation et d'Evaluation en Santé* (ANAES)[29], inviting them to reflect on :

- the content of information to be given to patients
- the need for information to be objective and validated. If the clinical trial involves a placebo control, it must be mentioned in the information supplied to the patient, and the person concerned must be made aware that there is one chance in two of receiving the placebo.
- the way of presenting the risks and their management. Information to individuals included in tests must be as exhaustive as possible and include the advantages, the constraints, and the drawbacks of participating in the trial.
- the need to make sure that information is comprehensible to all patients; that documents remain strictly informative and never aim to persuade; and that information be seen as part of the system of healthcare. These recommendations make it abundantly clear that information owed to the patient cannot be reduced to purely formal and administrative processes. It must

[28] CCNE: Opinion N° 55 (1997) Opinion On Information To Be Given To Patients Regarding The Possibility Of Transmission Of The Infective Agent Of Creutzfeldt-Jakob Disease By Blood Components. Available at: http://www.ccne-ethique.fr

[29] Information to patients – Recommendations to practioners (March 2000) Available at: http://www.anaes.fr

necessarily be a fully integrated part of the medical management plan and integrate the humanitarian aspect of the "*colloque singulier*" (a unique discussion between equals) ; **to that extent, interaction between the carer and the cared for makes *information* become *communication*, and this becomes a component part of understanding the pathology, and a token of adequate therapeutic compliance.** It would be sensible to consider that such arrangements which were initially developed for health caring, should naturally and significantly be extended to clinical investigation.

The above thoughts on the principle of precaution do not claim to be exhaustive. The subject is of much greater consequence than what is contained in these brief comments.

II. Cases of incompetence

II. 1. The problem of consent for a third party

As all research protocols are based on consent, when there is inability to consent, the issue of what should be done must be addressed.

Some time ago, CCNE proposed[30] a study on the feasibility of a system whereby everybody could designate a « representative » (or « agent » or « spokesperson »), who would be empowered to dialogue with doctors when the persons concerned were unable to express their wishes. CCNE also expressed an opinion on consent for the benefit of another person in the case of health care[31], or in the extreme case of "experimental therapies"[32]; but pure research has special characteristics[33] where the principle of the body's inviolate nature in the absence of medical necessity (therapeutic or diagnostic) predominates [34].

For « incompetent » patients and their legal representative, the difficulties of securing consent are similar to those encountered frequently in neurological, geriatric, psychiatric, and infantile pathologies, and in the whole range of care for the critically ill.

Such cases vary considerably; the following situations occur:

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[30] CCNE: Opinion N°58 (12th June 1998): Informed Consent Of And Information Provided To Persons Accepting Care Or Research Procedures. Available at : http://www.ccne-ethique.fr

[31] CCNE: Opinion N° 70 Consent for the benefit of another person. Available at: http://www.ccne-ethique.fr

[32] CCNE: Avis N° 71 Functional neurosurgery for severe psychiatric disorders". Available at :http://www.ccne-ethique.fr

[33] See CCNE Opinions N° 2 : Opinion on the testing of new treatments on humans. Considerations and proposals, N° 12, Opinion regarding medical and scientific experimentation on clinically brain dead subjects. Report, N° 57, Technical progress, health and societal models : the ethical dimension of collective choices, N° 58 Informed consent of and information to persons accepting care or research procedures, N° 73 Phase I trials in cancer . Available at: http://www.ccne-ethique.fr (access verified August 29 2003)

[34] It should be noted however, that the draft bill under examination by Parliament modifies article 16-3 of the *Code Civil*. The new drafting is as follows : « The integrity of the human body can only be violated in case of medical necessity for the person concerned or, in exceptional circumstances, in the therapeutic interests of a third party ».

- The case of minors, which deserves special attention[35]. Personal consent given by minors able to express their wishes, or refusal to give consent, or revocation of previously given consent, must absolutely be taken into consideration, and securing that consent is an ethical obligation not to be ignored.
- Specially protected persons, such as pregnant women[36].
- Wards of court (for their property but not their persons), or prisoners[37].
- Incompetents, whose chronic incapacity (brought about for instance by Alzheimer's disease) requires special protective measures;
- or persons for whom the urgency of starting research (which it is hoped would be of benefit to the patient…) is such that in practice, consent cannot be requested from anyone. According to article 209-9 of the Huriet Law, urgency was defined as when the patient « could not consent », which meant that the family (who became *de facto* the patient's « legal representative ») had to be asked for authorisation to carry out research. The corollary to that practice could very well mean that in the absence of any family, research could not begin.

This particular situation has been interpreted in a permissive and pragmatic manner by some doctors, to favour the authorisation of research, whereas for some legal experts, the law already prohibited this kind of research (i.e. before any consideration of provisions laid down by the European Directive). The European Directive seems to « lock-out » any « flexibility » for research in an emergency and states clearly that no derogation to **explicit and prior consent** by patients or by their « legal representative », including in an emergency, is allowed, so that research in effect becomes impossible in such cases. This position has been criticised by several scientific associations, and the classic examples of medical research on resuscitation after heart failure, or in neurotraumatology[38] were raised.

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[35] Article L. 1121-6 of the *Code de la Santé Publique*:
*"**Minors**, **adults protected** by law, and persons admitted into a sanitary or social institution for other reasons than research, cannot be approached for participation in biomedical research**, unless direct benefit for their own health can be expected** as a result*
***However**, research without direct individual benefit is acceptable if the **three** following **conditions** are satisfied*
- *it presents **no foreseeable serious risk** for their health*
- *it can be of assistance to persons presenting the **same characteristics** of age, sickness, or infirmity ;*
- ***it cannot be carried out in any other fashion. »***

Article L. 1122-2 of the *Code de la Santé Publique*:
When minors or adults protected by law are the subject of biomedical research :
- *Consent must be given, in conformity with the rules set out in article L. 122-1 of the present code, by the holders of **parental authority** for non emancipated minors. For minors or adults protected by law, consent is given by the **legal representative** for research **with** direct individual benefit which does not involve a **serious foreseeable risk** and**, in other cases, by the legal representative, authorised by the family council or by the guardian magistrate**;*
- *The consent of minors or of adulst protected by law must also be secured if they are able to express their wishes. Refusal or subsequent revocation of consent cannot be disregarded.*

[36] Pregnant women or nursing mothers: Article L. 1121-4 of the *Code de la Santé Publique*
*"Research **without** direct individual benefit involving pregnant, parturient, and nursing women are only acceptable if they do not entail **any serious foreseeable risk** for their health or that of their child, if they are **useful to gain knowledge about** pregnancy, delivery, or breast-feeding, and **if they cannot be performed in any other way.** »*

[37] Prisoners, the insane : Article L. 1121-5 of the *Code de la Santé Publique*
"Persons deprived of their freedom by judicial or administrative decision, patients in an emergency situation, and persons in hospital without their consent, by virtue of articles L. 3212-1 (on the request of a third party) and L. 3212-1 (compulsory admission to hospital) who are not protected by law cannot be approached for consent to participate in biomedical research, unless **direct and major benefit** to their health is expected. »

[38] *The Lancet* vol 361, 26th April 2003

In view of the impossibility of obtaining consent from patients themselves, and in spite of the existence in French law of the concept of legal representative, the issue of consent for or by another person remains a thorny one. One can observe on this point that the Directive does not dispel the ambiguities of the Huriet law since it admits that if « there are grounds for expecting…a benefit to the patient outweighing the risk», clinical trials on incapacitated adults not able to give informed legal consent are authorised (Art. 5 i). What is stated without equivocation is the need to obtain informed consent from the legal representative. Although there is « the subject's presumed will », there is no « presumed consent » in these circumstances.

The formulation proposed in the last paragraphs of article L-1121.1 of the draft bill regarding public health policy[39], seems to eliminate that ambiguity when it states:

> « In the case of biomedical research to be implemented on persons incapable of expressing consent, and who are not wards of court, the consent of a member of the family, or of a responsible person, must be secured before research commences.
>
> However, in cases of biomedical research to be implemented as a matter of urgency so that there is no possibility of securing prior consent from the person concerned, the protocol submitted for an opinion to the committee set up by article L.1123-1 of the present code, may provide that the consent of the person concerned will not be sought, and that only the consent of members of the family, or by default, the responsible person designated by article L.1111-6 in conditions outlined above, will be sought, **if they are present.**
>
> For the implementation of the two previous paragraphs, the person concerned will be informed as soon as possible, and his/her consent sought for possible continuation of that research. »

II. 2. Legitimacy of the representative – conditions

The concept of "capacity", which is awkward to define in legal terms, is also difficult to capture from philosophic or ethical viewpoints. Rather than the notion of "competence" which is always so difficult to consider from the various legal, medical, and cognitive viewpoints (and which refers to an institution or a body, and not to a person), perhaps one could introduce the notion of "capability", it being understood that the "capacity to act has no name[40]".

[39] First draft for the revision of articles L.1121-1 and the following regarding the protection of persons consenting to participate in biomedical research, and of articles L.5121-1-1, L.5124-1 and L.5126-1 incorporating in particular the transposition of directive 2001/20/CE regarding the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Version of March 27 2003, available at http://www.sante.gouv.fr/htm/dossiers/loi_huriet/huriet_avantprojet.pdf

[40] Aristotle states in this respect: "For instance, the name given to the runner or boxer, who is so called in virtue of an inborn capacity, is not derived from that of any quality; for those capacities have no name assigned to them. In this, the inborn

Since the new Committees for the Protection of Persons are to be more focussed on scientific expertise, there would be conformity with the principle of precaution (as considered in the present Opinion) if there were to be mediation between the patient and the research approved by these Committees. Indeed, from the point of view that sees the principle of precaution as a "procedural tool with which to go beyond the usual modes of consultation of experts and, more generally, to give back to actors in society the mastery of their own fate"[41], discussion regarding consent by those who are incapable should be broadened beyond the epistemological pertinence of the investigation. "Uncertainty requires the mobilisation of a diversity of knowledge and competence."

In situations where it is impossible to secure immediate consent from the patient, or the patient's family, or from a legal representative when there is one, because of urgency (as in the example of research on heart failure), the present clauses of article L. 1122-1[42] of the *Code de Santé Publique* (Code of Public Health) guarantee the protection of individuals, but do not offer the possibility of performing therapeutic trials in such circumstances unless an opinion is sought from a « responsible person » whose status is very ambiguous (attending medical practitioner, etc…). According to this article, it is possible to explain to a CPPR the reasons for which there is sometimes no other option except asking for the opinion of a member of the family or of the « responsible person », if one of these is present. If that article is maintained, continuing research in certain emergencies would be licit, contrary to an interpretation of the Directive to the effect that the only possible legal representative would be the guardian of incompetent adults. In order to cope with such situations, perhaps a proposal could be made to include the provisions of article L. 1122-1 into the European document.

Recognition of a concession of this nature in an emergency would permit the continuation of research activity, whilst maintaining balanced safeguards for the protection of individuals. However, the difficulty of the subject is such that a vigilant attitude is called for, which is recognised as necessary in the text of the Directive ("Member States shall, insofar as they have not already done so, adopt detailed rules to protect from abuse individuals who are incapable of giving their informed consent"). In fact, certain criticisms have been levelled because of the fear of a return to the "medical paternalism" implied by the notion of incapacity for such patients:

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capacity is distinct from the science, with reference to which men are called, e.g. boxers or wrestlers." (*Categories*, 10b1-5, tr fr, Seuil, 2002, p. 108-109), quote by A. Benmakhlouf, Séminaire de Réflexion du CCNE, June 2003.

[41] Hunyadi M., « Pourquoi avons-nous besoin du raisonnement de précaution ? », « (Why do we need the rationale of precaution?) op. cit. p.147

[42] Article L. 1122-1 of the *Code de la Santé Publique*:
Consent is given in writing, or if that is impossible, certified by a third party. The latter must be totally independent of the investigator and the sponsor. However, when biomedical research must be initiated in **cases of emergency** which do not allow for prior consent from the person concerned, the protocol submitted for an opinion from the committee set up by article L. 1123-1 of this code may provide that the consent of that person will not be secured and that only the consent of **members of the family**, if they are present, or by default, the opinion of the **responsible person** referred to in article L.1111-6 (law dated 4/3/2002) in the circumstances described above. The person concerned will be informed as soon as possible and his/her consent will be sought for the possible continuation of that research.

> « the argument consisting in stating that research on a patient under resuscitation and incapable of consenting is justified by the potential therapeutic benefit for future patients, does not appear to be correct; from an ethical point of view in this case there is opposition between the respect due to ONE patient, and the interest of ALL patients, with therefore the need to arbitrate between respect for a person and the interests of the community. »[43]

This point is specifically recognised in the present draft of the law which specifies that "the interests of persons accepting to participate in biomedical research always takes precedence over those of science and society"[44], thus extending the recommendations of the Directive for minors and adults incapable of expressing consent, to biomedical research generally, in compliance with the Declaration of Helsinki and the Oviedo Convention. In the United States, according to the FDA, exceptions regarding consent are possible in life-threatening cases requiring recourse to a test while the reference treatment has not been interrupted, incapacity of the patient, impossibility of obtaining timely consent from the legal representative, and finally absence of any alternative therapy offering the same chances of success.

Some research involving only « minimal » risk, does not require any special form of consent, « minimal » risk being defined as « risks not greater than those normally encountered in day-to-day life or when undergoing routine physical or psychological tests ».

The transposition of the European Directive therefore raises again the issue of the discrepancy between the absence of possible consent from a person and the possibility of carrying out research on that person in cases of emergency or prolonged incapacity. However, going further than initial precautions at the time of submission and verification of the pertinence of research, there is a need to differentiate between these two situations. In the second, the step of mediation for individual inclusion of patients (such as for instance research on Alzheimer's disease) will of course call on the family and the responsible person first of all, since they are obvious interlocutors in this process. However, emergencies are more stressful because frequently time is too short (no more than a minute in some situations) to get in touch with these natural protectors (for example research on resuscitation for heart failure). In these sometimes dramatic situations, the existence of an outside opinion independent of the investigator becomes very pertinent.

It is interesting to note for instance, that even in the case when consent by the person concerned is presumed (as in the case of organ donation), the physician is not exempt from seeking mediation and obtaining assurance from referendaries. This is all the more reason for not accepting the absence of such mediation in a situation where there is no presumption of consent (as is the case for biomedical research).

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[43] Position upheld by the working group on ethical issues of the French Society of Anaesthesia and Intensive Care *(Société Française d'Anesthésie et de Réanimation)* regarding the corpus of proposals for revision of the Huriet-Sérusclat law of October 2002. Availabe at : http://www.sfar.org

[44] Article L. 1121-2 of the draft bill regarding public health policy.

II. 3. Mediation

Incapacity cases demonstrate the importance of mediation in some medical situations. One of the conditions for validity of consent is to be certain that the information which has been communicated is fully understood. Mediation can then be a help and be validated, even in other situations besides incapacity; it goes beyond the broader realm of information to be given to the patient and is a part of the relationship of trust between doctor and patient.

There is also the issue of who is a suitable mediator.

Perhaps it would be better to consider that these are "mediating commissions" rather than a single mediator[45]. It will always of course be difficult in practice to convene people from outside to discuss the ethical quality of an item of biomedical research on a patient who is unable to consent explicitly. However, it is necessary to recall that the presence of a third party with a right to make sure that research is adapted to the interests of a patient, is the best guarantee of good practices. In any event, this presence of a third party should be restricted to "making present" the one whose state of health has, so to speak, "made absent from the world", momentarily or irreversibly, and to being able to say whether there is a risk that someone who is in a vulnerable state could become a victim of abuse.

Mediation represents an external, critical, and independent conscience whose presence gives a broader dimension to the debate. It implies two components: relationship and otherness. Relationship is defined in terms of "representation"; the mediator is the "representative", which quite literally means that he has the power to "make present" (*representare*) the one who is absent. By the words he speaks, the acts he performs, the contracts he signs, etc., he is committed to rendering the meaning of the words and exact nature of the intentions of the person he represents. Whatever formula is chosen, the mediator must never be mistaken for a substitute of the person concerned. "Whatever mode of protection is chosen, someone who intervenes for the person concerned *must never be a substitute for that person*; he *represents* that person, which is quite different. It is not the same thing to speak *in the name* of someone, and speak *in the place* of someone"[46]. To be someone's spokesman is to echo his interests and also his values. The case of organ donation is an illustration of the possible confusion between the aspirations of the person who is represented and the personal preferences of the representative. When members of a family are informed and attended to, and are asked to assent to the removal of the organs of their relative, the effort to speak in the place of the deceased becomes a statement based on knowledge of the values to which the deceased subscribed.

[45] Kourilsky-Viney report, op. cit. p.2
[46] D. Thouvenin, Directrice du Centre d'Etudes du Vivant (Université Paris VII Denis Diderot)oral communication.

Mediation would therefore be seen as a missing link in a conscience, not as someone who takes a decision, but as someone who dignifies a debate by imposing its necessity.

Be that as it may, it is quite clear that, neither the responsible person, nor the mediator, nor mediation itself, can solve those issues arising out of an emergency that fall within the human responsibility of the investigator.

III. The reform of the CCPPRBs (IRB)

Scientific supervision of research is necessary. If specialised committees are created by drawing on medical scientific associations, for example, there is a risk of arriving at research where themes and supervision would be entirely in the hands of scientific peers, and the social component of supervision of research would be lost. However, CCNE welcomes a reinforcement of the role of CCPPRBs (Institutional Review Boards). Once they are adapted and reinforced, their task could be seen as an extension of responsibility to include an evaluation of the pertinence of research, of its scientific design, of whether the weighing of expected benefits and risks is satisfactory, of how well founded are its conclusions, since long term monitoring, and the publication of even negative results, would encourage research to be transparent. Following the Directive[47], the considerations of the future draft bill concerning public health policy, underline:

> "on the one hand, that the evaluation of ethical acceptability cannot be dissociated from evaluation of the scientific pertinence of a research project, and on the other hand, the evaluation of the foreseeable benefit/risk balance is the essential criterion for the evaluation of research. In addition, when it evaluates the consent securing procedures, the committee decides whether it is necessary to provide for a waiting period between the supply of information to the subjects and consent. There would be particular justification for this when decision to participate is difficult, especially when other medical alternatives are available".

It is in fact the multidisciplinary aspect which helps to adjust with greater precision the mandatory requirements for prerequisites and the evaluation of the competence of the investigator. The evolution of CCPPRBs, who cease to be purely consultative, since in their new role as "Committees for the Protection of Persons involved in Research" (CPPR) they must give reasoned opinions which regulating or supervisory authorities would be guided by, is in fact the **only possibility of maintaining a critical and ethical eye on proposed research**. Increased attention to the evaluation of the benefit/risk balance helps to gain recognition of the preponderant role of the principle of proportionality of Public Law in medical analysis. This proportionality cannot be recognised by the person carrying out research (or by the scientific association which may be associated in the research), so that it is up to the CPPRs to act as mediators between researchers and subjects of research, by taking

[47] Article L. 1123-7 of the draft bill concerning public health policy.

on further responsibilities, without of course overreaching their extended mission. There is a need to be absolutely precise in the delimitation of those responsibilities, so that action is not paralysed by ambiguities regarding its legal status. In any event, this vision of new responsibilities must also be supported by financial resources for action, training, and compensation for the work performed.

Extending the mission of CPPRs, in particular as regards scientific expertise, requires new provisions so that they can take on their new responsibilities within the stipulated time frame. In the case of negative findings, there should be a possibility of appealing their decisions.

New and very particular attention should be given to the benefit/risk question which sometimes raises major ethical problems. For example, a therapeutic research protocol requiring financial resources out of all proportion to the expected benefit should not be undertaken.

This new view of clinical research must, by definition, conform to the corpus of "good clinical practices". To comply with requirements for independence and non-subordination, perhaps there should be a proposal to exclude (from decision, and not necessarily from instruction and consultation) the ethical bodies attached to scientific associations and the CPPRs of the health care centre where research is to be carried out. There should be much more precision also as regards correspondence in timing between the opinions requested from AFSSAPS and the CPPR, so as to avoid redundancy and delay.

A difficult ethical issue remains to be solved: the internationalisation of research. It would be wrong to set up exaggerated obstacles akin to legislative harassment, to the detriment not only of France's contribution to research, but also as regards the very real issues of respect for persons. There is no reason to be more demanding than the European Directive as regards deadlines for replies or excessive inflexibility. What is important is that action should be transparent, rather than to construct complex procedures which are difficult to apply. Transposition of the European Directive on research must not elude the issue of research carried out by countries of the North in countries of the South. There is no reason why a different approach should allow the Directive to be limited in geographical scope. CCNE's opinion on this subject (Opinion n°78) draws attention to its importance.

IV. The question of the definition of the scope of biomedical research in the European Directive.

The European Directive applies to "clinical trials on medicinal products"; it is not concerned with physiopathological and cognitive research. The Huriet Law covers biomedical research in a broader sense. In particular, it mentions research in "the behavioural sciences" for which provisions regarding consent had in fact already been specified in the 1994 revision. Transposition of the European Directive raises therefore, as regards the Huriet law, the question of the ethical monitoring of research on humans when it is not strictly speaking a "trial on medicinal products". Although some research in the field of behavioural sciences are also directly concerned with biomedical research (e.g. in neuropsychology), this is not so in the majority of cases.

Examination of this kind of research by CPPRs could therefore be a problem, in particular because of the numbers and subjects of the cases submitted for examination. There would also be a need concomitantly for an adjustment of the scientific competence of the present CCPPRBs, which are not composed of experts in the behavioural sciences as such, and they would furthermore have to be able to refer to a CCPPRB (whereas at the present time, only a physician is authorised to do so).

Nevertheless, it would be right to submit behavioural research projects, in the same fashion as biomedical research – and probably any kind of research – to ethical supervision. It has however already been suggested[48], in a review of a report written in 1998 by the CNRS (*Centre National de Recherche Scientifique*: the French National Centre for Scientific Research)[49], that it would appear that constraints applied to biomedical research are more often than not inadequate for behavioural research. In 1993[50], CCNE had already formulated some proposals on this subject. They could serve as a basis for setting up ethically and scientifically adequate provisions for this field of research.

Conclusion

In conclusion, CCNE's main points of emphasis in this Opinion are the following:

The "benefit/risk" balance replacing the "with or without direct benefit" concept, has the advantage of dispelling certain ambiguities and does not raise any particular ethical problem since it is compatible with the principle of respecting the person. It has for that matter been approved by international consensus.

Situations where a person is unable to consent, whatever the state of his/her health, can never be settled easily by the resort of asking the consent of a third party, which is frequently an impossibility anyway apart from the exceptional cases already listed by law. Although such situations do exist and research needs to be done in those circumstances, only the meticulous attention of a CPPR to the question of the interests of the person concerned, is relevant. The notion of collective interests cannot be taken into consideration unless the person concerned would seem, *a priori*, not likely to suffer any prejudice. Emergencies, when no third party is present, should allow that some cognitive research without prejudice to the patient be performed without excessive constraints. However, if there is any risk of prejudice, that risk cannot be entertained unless a CPPR carries out an in depth examination of the legitimacy of such action, and therefore provides essential guarantees that the whole range of

[48] Caverni J.-P. *L'éthique dans les sciences du comportement,* (Ethics in the behavioural sciences) PUF, coll. Que sais-je?, 1998

[49] *Le contrôle éthique de la recherche comportementale chez l'homme*, (Ethical supervision in behavioural human research, Report by the Group"Sciences du comportement humain" , Copé, October 1998

[50] CCNE: Opinion n° 38 (October 14th 1993) on the ethics of research in the sciences of human behaviour.. Available at : http://www.ccne-ethique.fr

opinions will be reviewed, and not purely the interests of researchers, as could be the case for committees specialising in a single discipline.

To sum up, to prohibit all research on the grounds that consent is an impossibility would be devoid of sense when the risk to the patient is puny or when other categories of persons could not be the subject of that research. It would not however be ethical to use the fact that consent was not possible as a way of facilitating research. A prior check is therefore needed, and it would seem that only CPPRs would be able to carry it out.

Research on healthy volunteers, where by nature, the benefit/risk balance can only be negative, should continue to be the subject of special attention, specific to that type of research and radically different from the procedure for research on the sick.

The extension of the competence of CCPPRBs, who would cease to be "consultative" and would become "Committees for the Protection of Persons involved in Research" should be seen as an improvement, and the task they have been given becomes of major importance because of the commitment to protect the interests of persons.

The essential point which remains to be seen as regards cognitive and therapeutic research involving humans is that of respect for the person coming before possible constraints imposed by scientific progress. However, there is no example of therapeutic progress which was not at some point based on a certain degree of constraint. This is in fact the very contradiction which postulates that researchers always remain aware of not only their scientific responsibilities but also of their responsibilities to humanity.

On the one hand, the absence of consent has perhaps restricted research in situations where cognitive functions were lacking, and in this regard, there is some part of medical research, which is bound by irrevocable constraints. On the other hand, for a person unable to consent, access for medical research with a cognitive or therapeutic purpose must not be taken for granted without a reinforcement of protection.

That conflict defines the ethical dilemma. How do you protect people from recklessness and unbridled science? Submitting potentially controversial protocols to CCPPRBs, whose decisions must be wise in proportion to the extension of their powers, should make it possible to take into consideration the motivations of scientists and their capacity to make public opinion aware of their sense of responsibility. "Consent" is never unconditional; "to be unable to consent" may well remain a real obstacle to medical research. What must be avoided above all is purely formal consent designed to protect the institution rather than the individual.

September 18, 2003