

# Committee for the Protection of Persons

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## Abstract

The transposition into French law of Directive 2001/20/CE, which relates to good clinical practice in the conduction of trials on drugs for human use, has required the modification of certain provisions that concern the protection of persons participating in biomedical research, in particular those provisions concerning the conditions for the authorisation of biomedical research. Declaration to the competent authorities now comes prior to authorisation and, henceforth, the prior opinion of a Committee for the Protection of Persons (CPP) must be expressly favourable in order for a trial to be undertaken.

Proposals are put forward by this Round Table in order to promote the stability and professionalism of the CPPs.

**Keywords:** Committee for the Protection of Persons (CPP), biomedical research, clinical trials, legislation

Bill no. 88-1138 of 20 December 1988<sup>[1]</sup> relating to “the protection of persons participating in biomedical research” created a new structure in public health law, the Consultative Committee for the Protection of Persons in Biomedical Research (CCPPBR).

The transposition into internal law of Directive 2001/20/CE<sup>[2]</sup> of 4 April 2001, which concerned “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”, gave legislators an opportunity to considerably modify the legislative provision called the *Huriet-Sérusclat Law*, notably with regard to the independent committee mentioned above.

Bill no. 2004-806 of 9 August 2004<sup>[3]</sup> established the Committees for the Protection of Persons (CPPs), whose opinion with regard to a biomedical research project must be favourable for the project to be undertaken. In parallel, the administrative procedure of a declaration of intent prior to performing research, incumbent upon the sponsor, is replaced by an authorisation from the competent administrative authority.

The Bill includes changes to the responsibilities, roles and composition of the Committee. The latter issues, in particular, a ‘reasoned opinion’ ensuing from missions set out in the Bill. This opinion may be contested.

This Round Table, whose exact title was “the Committee for the Protection of Persons: Role with regard to Sponsors, to the Regulatory Authorities and to Patients; Organisation in the context of clinical trials on drugs”, had as its aim to examine these different aspects and restricted itself solely to the situation of clinical trials on medicinal products. It took place in the period between the publication of the Bill of 9 August 2004<sup>[3]</sup> and that legislation coming into force. The aim of this article is not to report the content of the discussions of the Round Table, but to provide a synopsis of the discussions and the conclusions presented in the plenary session, after approval by the members participating in the Round Table.

## 1. Preparatory Work

Prior to holding the Round Table, during the 20th Journées de Giens from 3 to 5 October 2004, meetings were organised and the prospective members who were to participate were divided into four subgroups. Each subgroup was in charge of examining one particular aspect of the proposed subject.

- *Subgroup 1:* Role of the CPP before the implementation of a biomedical research project;
- *Subgroup 2:* Role of the CPP during and after a biomedical research project;

\* For a list of participants, please see the end of the article.

1 All legislation mentioned in this article can be found at <http://www.legifrance.gouv.fr>.

- *Subgroup 3*: Responsibilities of the CPP;
- *Subgroup 4*: Organisation of the CPP.

Apart from their own experience relating to CCPBPRs, the members of each of the subgroups had at their disposal the following reference texts:

- the European Directive 2001/20/CE of 4 April 2001,<sup>[2]</sup> mentioned above;
- Bill no. 2004-806 of 9 August 2004<sup>[3]</sup> modifying the *Huriet-Sérusclat Law*;
- detailed information issued by the European Commission called *Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial* (April 2004 version);<sup>[4]</sup>
- detailed information issued by the European Commission called *Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on a medicinal product for human use* (April 2004 version).<sup>[5]</sup>

In order to attempt to prevent any subsequent digressions, the restrictive nature of the title was emphasised. The matter at hand was restricted to the situation of a clinical trial as defined by the above-mentioned European Directive: “any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy”.

The expression “biomedical research” in French law covers, in fact, a much larger field of scientific inquiry than the clinical trial on a medicinal product.

For a clinical trial, the competent authority is the Agence française de sécurité sanitaire des produits de santé (Afssaps), the French Agency for the Health Safety of Healthcare Products.

It should be remembered that, in the terms of the Directive, a ‘non-interventional trial’ does not constitute a clinical trial, but “a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data”.

## 2. Examination of the Situation of the Committees for the Protection of Persons (CPPs)

### 2.1 Role Prior to the Trial

Prior to performing biomedical research in human subjects, the sponsor is required to submit the project to one of the competent CPPs that are responsible for the region in which the investigator, or the coordinating investigator if the case arises, carries out the research. The sponsor may request only one opinion per research project (article L1123-6 of the Code of Public Health [CPH]<sup>[6]</sup>). The Committee gives its opinion on the conditions of validity of the research project (article L1123-7 CPH<sup>[6]</sup>), notably with regard to:

- “the protection of persons, particularly the protection of trial subjects;
- the adequacy, completeness and intelligibility of the written information to be given and the procedure to be followed for the purpose of obtaining informed consent and the justification for research on persons incapable of giving informed consent;
- the possible necessity for a period of reflection;
- the possible necessity to make provision, in the protocol, for prohibiting subjects from participating simultaneously in another research project or to impose an exclusion period;
- the relevance of the research project, whether the evaluation of the anticipated benefits and risks is satisfactory and whether the conclusions are justified;
- the suitability between the objectives and the means to be employed;
- the qualifications of the investigator(s);
- the provision for and amount of indemnities for trial subjects;
- the provisions for recruitment of trial subjects;
- the possible need to set up an independent supervisory committee, on the initiative of the sponsor, the presence or absence of which the latter must promote.”

The Committee must also ensure that:

- the facility where the research is to be performed has the administrative authorisation, if the case arises, in conformity with the regulations in force, issued by the state representative in the region after it has been verified that the human, material and technical means appropriate for the research project exist and are compatible with safety requirements (article L1121-13 CPH<sup>[6]</sup>);
- the possible amendments made to the research protocol at the request of the CPP have been communicated to the competent administrative authority (article L1123-7 CPH<sup>[6]</sup>).

In accordance with regulations (articles L1123-7 and L1243-3 CPH<sup>[6]</sup>), the Committee must also be approached if:

- a collection of biological samples is put together (i.e. the bringing together of, for scientific ends, biological samples taken from a group of persons identified and selected on the basis of the clinical or biological characteristics of one or several members of this group);
- elements or products of the human body are used for scientific ends when this involves a substantial change in the final purpose with regard to the consent initially given by the donor at the time of the collection of the elements or products.

Finally, in the case of a trial designed to evaluate standard care, in which the acts are performed and the products (with the exception of those mentioned in article L5311-1 CPH<sup>[6]</sup>) are used in the usual manner, but where particular provisions are made for supervision, a protocol describing these particular provisions and the conditions for informing the persons concerned must be written and submitted to the CPP for prior opinion. The regulations do not, in this case, provide for a necessarily favourable opinion.

The role of the CPP is particularly important with regard to the consent of persons invited to participate in a research project and the information provided to them both before and after the trial. In this respect, the Round Table group proposed a standard list of what should be contained in the information given to persons who participate in a research project (table I). The regulations provide that the person “has the right to receive communication, during or upon completion of the research project, of information concerning his/her health”, that is in the possession of the investigator, and he/she has the right to be informed of the overall results of this research, in accordance with the provisions that must be set out in the information document. The Committee must ensure that such provisions exist.

When biomedical research is specifically aimed at or is likely to concern minors or persons of an age under guardianship or supervision, the Committee may request that reinforced protective measures be implemented. These may include securing a guardianship judge if the Committee considers that the research project involves a serious risk to privacy or the integrity of the human body because of the constraints the project imposes or the interventions it entails. The same is true in the case of persons of age who are incapable of giving their consent but are not under any form of legal guardianship.

Because the regulations make provision for the compilation of a national registry of persons who do not have any medical condition who participate in research projects or patients who participate in research projects concerning a medical condition they do not have, the Committee may decide that, given the risks and constraints involved in a research project, persons participating in this research project should be included in the registry even though they do not belong to either of the categories above.

**Table I.** Information prior to obtaining consent

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Title, sponsor, aim, objectives, nature of products, notion of research
Names and occupations of investigators (and clinical staff)
Nature of trial subjects: number and characteristics of subjects included
Trial conduct: methods, medical acts, visits
Specific constraints of the research project: number of visits, admissions and samples, quantity of samples taken, specific investigations, duration of participation
Potential risks/expected benefit
Alternative treatment possible
Follow-up after trial completion: continuity of treatment
Period of reflection
Duration of exclusion period
Possible inclusion in the national registry
Freedom to participate, right to withdraw consent, absence of harm and of responsibility, preservation of rights
Name and address of the investigator/right to ask questions
Information and additional consent in view of new information
Insurance of sponsor
Indemnities: what, how much and how to claim?
Access to overall results
Right of access to and correction of CNIL database
Confidentiality/anonymity of documents/publication
Persons authorised to consult data
Opinion of CPP
Point of contact
Circumstances or foreseeable reasons that could lead to discontinuation of subject's participation

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**CNIL** = Commission Nationale Informatique et Liberté; **CPP** = Committee for the Protection of Persons.

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In this phase prior to the possible implementation of a clinical trial by a sponsor, the Committee may receive from the competent administrative authority protocol amendments that it has requested from the sponsor when it raises objections to the implementation of the research project.

In parallel, the Committee informs the competent authority of any protocol amendments it has requested.

## 2.2 Role During and After the Trial

The CPH<sup>[6]</sup> provided that: “The CCPPBR may issue ... an opinion favourable to the conduct of a research project, on the condition that the sponsor provides additional information during the conduct of the trial. Upon receipt of the information, the Committee may uphold or modify its opinion.” This capacity is not extended to the CPP.

Nevertheless, during the trial “any substantial modification of (the research project) on the initiative of the sponsor must obtain, prior to its implementation, a favourable opinion from the

Committee and authorisation from the competent authority. In this case, the Committee ensures that additional consent has been obtained from the persons participating in the research project, should this be necessary" (article L1123-9 CPH<sup>[6]</sup>).

Similarly, "the adverse reactions and events defined for each type of research project are reported respectively by the investigator to the sponsor, and by the sponsor to the competent authority as well as to the competent CPP. In this case, the Committee ensures, if necessary, that the persons participating in the research project have been informed of the adverse events and that they have confirmed their consent" (article L1123-10 CPH<sup>[6]</sup>).

According to the European Directive, these defined adverse reactions and events are serious unexpected adverse events and those resulting in death. Seriousness is evaluated by the fact that the event results in death, is life threatening, requires hospitalisation or prolongation of hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. Adverse reactions are distinguished from adverse events by establishing a probable causal relationship between it and the medicinal product being investigated. An adverse event may simply be a phenomenon observed in the course of the research project and may not have a causal relationship with the treatment. The unexpectedness of a reaction arises from the fact that its nature, severity or course is not consistent with the applicable product information (e.g. for an unauthorised product, the investigator's brochure).

The sponsor also informs the CPP of any new event relating to the trial or the medicinal product being investigated where that new event is likely to affect the safety of the subjects and informs the CPP of the possible safety measures being taken in such a situation. In professional practice and certain administrative guidelines the term 'new event' is understood to include, for example, the occurrence of serious unexpected adverse reactions involving the medicinal product being investigated in circumstances other than those of the trial under consideration, the results of interim analyses relevant to the safety of trial subjects (notably insufficient efficacy), the results of studies performed in animals that bring to light new information concerning the safety of the product and, in general, any new information that might lead to reassessment, in an unfavourable light, of the benefit/risk ratio of the research project (our emphasis). Moreover, the new event may relate to the situation of the trial and not specifically to the product being investigated.

The European Directive<sup>[2]</sup> mentioned above makes provision that, once a year "and throughout the clinical trial", the sponsor shall provide **to** the Member States in whose territory the clinical trial is being conducted and **to** the Ethics Committee (a term used in the European texts but whose official definition is not in-

compatible with the concept of the CPP) a list of all suspected serious adverse reactions that have occurred during the applicable period and a report of the subjects' safety. Communication of this document to the CPP is authorised even though this is not mentioned in the French regulations.

The provisions for the exchange of information between the competent authority and the Committee are to be defined, whether this concerns substantial modifications to the protocol, new events apart from emergency situations or serious adverse reactions (table II).

Considering the missions of Afssaps in terms of 'safety surveillance' and taking up the European detailed guidelines,<sup>[5]</sup> the group proposes that the Committee be forthwith informed of:

- serious unexpected adverse reactions occurring in France, on a case-by-case basis;
- other serious adverse reactions on a 6-monthly basis, in tabulated format, with a summary analysis.

This last point ensures that the Committee is periodically informed of the nature of these other related unexpected serious adverse reactions after causality assessments have been performed, which implies unblinding in comparative trials (an action most methodologists consider questionable) in the course of the trial, unless special precautions are taken.

Events should be distinguished from reactions, an event being characterised simply by its occurrence, while a reaction is an event for which a causal relationship with the research project or with a drug has been established.

A comment on this matter: the European Directive<sup>[2]</sup> mentioned above retains the principle of a causal relationship with the product being investigated, while the French regulations are concerned with the causal relationship with the trial situation.

Finally, the Committee must be informed, within a timeframe to be determined from a regulatory standpoint, either of the end of the trial at its planned term or of the reasons for early termination.

### 2.3 Responsibility of the CPP

According to the analysis performed by Joël Moret-Bailly, Vincent Diebolt and Thomas Roche, the jurists who made up subgroup 3, it appears that the role and definition of the responsibilities of the CPPs may not be established until they have been put into perspective. The European regulations relating to Ethics Committees and their transposition to the French law in the form of CPPs should not lead to replication in Europe, as in France, of the Institutional Review Boards seen in the US.

Furthermore, each legal concept is integrated and interpreted in the context of the system to which it belongs. The CPPs come

**Table II.** Afssaps and CPP missions and information exchange during the trial

Proposals	
Safety surveillance: roles of Afssaps and CPP	Afssaps defines the general strategy and in the case of 'new events' the general principles that should be applied CPP with the sponsor organises the implementation of safety surveillance procedures in the various studies
Information exchange Afssaps–CPP–sponsor	
amendments to trial protocol	Same operating procedure as for the initial application (i.e. parallel submissions, direct contact between CPP and Afssaps, with copy to sponsor) Afssaps 'coordinates' summary response to the sponsor on the condition that the initial deadline of 35 days is respected. (However, there is a possibility that the CPP will have a different deadline and/or a divergent evaluation to the Afssaps.)
new events	Transmission of information in parallel to CPP and Afssaps (another possibility: transmission from Afssaps to sponsor with copy to CPP) If necessary, Afssaps defines the general principles that are to be implemented and discusses these with the sponsor; the CPP checks on the sponsor's implementation of these (CPP checks additional memoranda, amendments, etc.). A procedure should be in place for when the request for modification is contested
SUSAR	Suggested 6-monthly listings Declaration for the comparator product?

**Afssaps** = Agence française de sécurité sanitaire des produits de santé; **CPP** = Committee for the Protection of Persons; **SUSAR** = suspected unexpected serious adverse reaction.

under 'administrative law', a concept that is nonexistent, for example, in the English-speaking world. The opinion of a CPP, provided for in the Bill of 9 August 2004,<sup>[3]</sup> included in the CPH,<sup>[6]</sup> comes under the general regulations relating to the administrative procedure for consultative opinions.

It should be remembered that the law, when it does not create its own concepts, lends a particular meaning to words, in keeping with its own logic and the goals that it pursues. Thus there is a high probability that the notions of 'opinion', 'validity' and 'relevance' that are found in the legal texts relating to the missions of the Committees differs, for jurists, from the meaning that may be given to them in everyday language, indeed in the language of biomedical research professionals. However, a law is interpreted by the standards of the law.

A number of administrative decisions are taken following consultation with the competent authorities responsible for giving their opinion on a technical question or the relevance of a forthcoming decision. In this context, an 'elementary' definition currently accepted by jurists holds that 'opinion' is a term "that applies in all branches of the law as the result of consultations whether compulsory or facultative, requested by a wide range of organisations, i.e. persons or commissions, boards, qualified public servants, the State Council, etc".<sup>[7]</sup> In this context, there are three types of administrative opinions: simple opinions, compulsory opinions and reasoned opinions.

Simple opinions, the first type, remain at the discretion of the administrative authority, which may or may not seek them, with no effect on the legality of the decision. Compulsory opin-

ions, the second type, are, as their name suggests, imperative if the decision is to have authority, in that it may not ordinarily dispense with the opinion. However, the decision is not bound by the opinion. In other words, a decision may be made that is contrary to the opinion with no consequence regarding the legality of the decision. The third type, reasoned opinions, are not only compulsory but also binding on the administrative authority with regard to the decision. Thus the authority only has two options: to make a decision in line with the opinion or to renounce the planned decision.<sup>[8]</sup>

In this context, the opinions of the CPPs belong to the third category, reasoned decisions. The Directive of 4 April 2001<sup>[2]</sup> in effect provides, in article 6, that the Committee "shall give its opinion, before a clinical trial commences, on any issue requested", making it compulsory. However, it also provides, in article 9, that "the sponsor may not start a clinical trial until the Ethics Committee has issued a favourable opinion". Article 88 of the Bill of 9 August,<sup>[3]</sup> codified in article L1121-4 CPH,<sup>[6]</sup> transposes this norm and provides that "the biomedical research project may not be implemented until the Committee for the Protection of Persons has issued a favourable opinion [...] and the competent authority has granted an authorisation". However, the Directive imposes a maximum period of 60 days for the Committee to inform the sponsor and the competent authority of its opinion. It also provides that the competent authority can notify the sponsor before the end of this period that it has no grounds for non-acceptance. In addition, the Directive provides that the competent authority may lay down a shorter period than 60 days

within their area of responsibility “if that is in compliance with current practice”.<sup>[2]</sup> As a result of this, the competent authority may choose to make a decision to authorise a trial without knowing the opinion of the Committee, and this is in accordance with EU regulations.

This qualification is important with regard to the legality of the trial. The role of the administration resides, in effect (as much politically as legally in French law and inasmuch as it is an emanation of the executive power) in the application of the law, itself an embodiment of the general will, neither more nor less, even though this role may lead it to produce legal norms of application itself. In a political context such as this, the administration can only be placed under the control of the citizens since the latter are at the origin of the law. Thus it is understandable that administrative decisions (and favourable opinions are comparable to these) may be subject to legal recourse intended to cancel illegal acts. This is called “recourse for excess of power” and is exercised before the administrative courts of law (i.e. the administrative court, the appeal court and State Council). Such a case, if it is founded, results in the annulment of the administrative decision, which is then supposed to have never existed. The possibility of litigation intended to protect legality is opened to everybody concerned by the decision, individuals or artificial persons, other administrations, taxpayers, etc.

It may be said, *in fine*, that if a favourable opinion is not received the research project is illegal and the competent authority, Afssaps, cannot authorise a research project that has received an unfavourable opinion from the CPP. On the other hand, the competent authority can refuse to grant authorisation to a research project that has received a favourable opinion, notably for reasons of public health enforcement. Inversely, it can formulate recourse for excess of power against an unfavourable opinion from the CPP.

However, the extent of the CPP’s control over research protocols has yet to be determined, notably with regard to their ‘validity’ and ‘relevance’, since the law confers this mission upon them.

Article L1123-7 CPH<sup>[6]</sup> provides, since 9 August 2004, that “the Committee gives its opinion on *the conditions of validity of the research project*, notably with regard to: the protection of persons, notably the protection of the participants; the adequacy, completeness and intelligibility of the written information to be given and the procedure to be followed for the purpose of obtaining informed consent and the justification for research on persons incapable of giving their informed consent; the possible necessity for a period of reflection; the possible necessity to make provision, in the protocol, for prohibiting subjects from participating simultaneously in another research project or to impose an exclu-

sion period; *the relevance of the research project*, whether the evaluation of the anticipated benefits and risks is satisfactory (evaluation performed by the sponsor) and whether the conclusions are justified; the suitability between the objectives and the means to be employed; the qualifications of the investigator(s); the provision for and amount of indemnities for the participants; the provisions for recruitment of the participants” (our emphasis).

In this context, the concept of ‘validity of the research’ does not pose any real legal problems. Indeed, in law, the term ‘validity’ takes on a very precise meaning: the absence of being contrary to hierarchically superior norms. Thus it is a question of ensuring that the conditions of the research project are not contrary to legal regulations. Moreover, it is to the latter that the remainder of this text refers. Therefore, the mission of the Committee resides in giving an opinion on the following question: Do the conditions of the research project comply with the regulations and thus protect the persons involved?

In this perspective, only the question of the scientific relevance of the research project proves to be delicate. The regulations provide that the Committee carries out its mission with regard to “*the relevance of the research*, whether the evaluation of the anticipated benefits and risks is satisfactory and whether the conclusions are justified the suitability between the objectives and the means to be employed” (our emphasis). Is the Committee transformed by this fact into an expert committee in charge of assessing the scientific relevance of the undertaking? The response, much discussed within the Round Table, is without a doubt negative. Indeed, apart from the preceding argument, according to which the validity, in a legal utterance, must be understood as not being contrary to a superior legal norm (and not, for example, a scientific norm for which we do not see, which cannot be superior or inferior to a rule of law, as it is not of the same nature), it is doubtful that a CPP could bring together all the necessary competence to cover all areas of research, especially in the most advanced scientific areas. Practically, indeed prosaically, the CPPs cannot be expert committees, although the temptation to conclude this is great, given the presence of biomedical research professionals within the Committees. However, there is nothing to stop the Committees from calling on scientific experts or others to elucidate their discussions.

In order to be completely convinced, we could put forward comparative arguments. To do this, let us take the example of indemnities for medical accidents, nosocomial infections and ‘therapeutic hazards’ as set out in the Bill no. 2002-303 of 4 March 2002<sup>[9]</sup> relating to the rights of patients and users and the healthcare system. Notably, the latter creates regional commissions for indemnification of medical accidents (CRCIs), which are responsible for giving an opinion to the National Office for

Indemnification of Medical Accidents (ONIAM) on the origin of the injury or damage to be compensated. It has been legislated that the CRCIs must include healthcare professionals. However, the commissions do not constitute expert advisors. The proof of this is that they give their opinion only after having heard an expert report. Why then are healthcare professionals included in these structures? Apart from the politically sensitive aspect of the question, which has led professionals to be associated in the procedure, the reason is that they have the capacity to understand, better than others, the information under consideration, especially the expert reports.

The same reasoning should be used with regard to the CPPs. Research professionals appear on the CPPs. Apart from historical reasons (the first 'ethics committees' were set up on the initiative of, and were made up of, professionals<sup>[10]</sup>), the reason for this is that research professionals are able to understand the protocols presented to CPPs. In other words, there is no question of the CPPs exercising in-depth scientific control over the research protocols. This is the prerogative of the competent authority, which for its part is responsible for public health enforcement and has at its disposal the means to cross-check information as well as call on experts when necessary. The CPPs are there to verify that trial protocols do not violate the law (and/or any scientific principle that might be obvious to research professionals) bearing in mind the aim of the law itself (which inspired the name of the committee): the protection of persons.

Two articles deserve special attention:

- If a Committee gives an unfavourable opinion, the sponsor may request that the Minister of Health submit the research project to another committee for a second examination, in accordance with the conditions set out in the regulations (article L1123-6 CPH<sup>[6]</sup>).
- If the Committee is at fault in the exercise of its mission, the responsibility of the State is instituted (article L1123-8 CPH<sup>[6]</sup>).

## 2.4 Organisation of the CPPs

### 2.4.1 Observations

The Bill of 9 August 2004<sup>[3]</sup> introduced new information concerning the CPPs with regard to their predecessor the CCPPBR.

Article L1123-1 CPH:<sup>[6]</sup>

"The Minister of Health registers at the regional level for a determined period of time one or, depending on the need, several Committees for the Protection of Persons and determines their territorial competence. The members are named by the State representative in the region.

The Committees are totally independent in the exercise of their mission. They are endowed with the legal status of a person."

Article L1123-2 CPH:<sup>[6]</sup>

"The Committees are formed in such a way as to ensure their independence and the diversity of competencies in the biomedical domain and with regard to ethical, social, psychological and legal questions. They have, among their members, designated representatives of registered associations of patients and of users of the healthcare system."

Article L1123-3 CPH:<sup>[6]</sup>

"The members of the Committees, the persons called upon to collaborate in their work, and the agents coming under the general status of public servants who are registered depositories thereof are legally bound, under the conditions and the penalties provided for in articles 226-13 and 226-14 of the Penal Code, to keep secret any information which comes to their knowledge by reason of their function and which is related to the nature of the research, to the persons who organise it or who participate in it, or to products, objects or experimental methods.

At the time of their nomination, the members of the Committees declare to the State representative in the region, their direct or indirect ties to the sponsors and investigators in the research project. This declaration is made public and updated on their initiative as soon as any change takes place concerning these ties or should new ties be established.

Persons who are not independent of the sponsor and the investigator in the research project under examination may not legitimately take part in the deliberations."

Article L1123-4 CPH:<sup>[6]</sup>

"The operating costs of the Committees are financed by the proceeds from a fixed fee paid by the sponsors for each biomedical research project that is the subject of a request for an opinion. The amount of this fee is fixed by the Minister of Health."

Article L1123-5 CPH:<sup>[6]</sup>

"The Minister of Health may withdraw the registration of the Committee if the conditions of independence, of formation or of operation necessary to carry out its mission are no longer satisfied."

The provisions for the application of the measures mentioned above will be set out in a decree of the State Council, which was in the process of being written at the time of the Round Table.

This is the case in particular of article L1123-14 CPH:<sup>[6]</sup>

"1° The composition and the conditions of registration, of financing, of operation and of nomination of the members of the Committees for the Protection of Persons, as well as the nature of the information that is to be communicated by the sponsor and upon which they are assigned to give their opinion;

2° The duration of registration of the Committees for the Protection of Persons;

3° The nature of the information that is to be communicated by the sponsor to the competent authority, in the application for authorisation mentioned in article L. 1121-4;

5° The provisions for the presentation and the contents of the application for modification of the research project provided for in article L. 1123-9;

7° The nature and the seriousness of the events and reactions that are notified as well as the provisions for this notification;

8° The provisions according to which the sponsor informs the competent authority and the Committee for the Protection of Persons of the end of the research project;

9° The provisions for evaluation provided for on the basis of the system of evaluation set out by the National Agency for Certification and Evaluation in Public Health and published by decree of the Minister of Health;

11° The periods within which the Committee gives the opinion mentioned in article L. 1123-7 and the competent authority issues the authorisation mentioned in article L. 1123-8.”

Experience acquired thanks to the CCPPBRs leads us to hope that certain administrative aspects of their operations will be reinforced, inasmuch as the Committee has the status of a person under public law, and that its opinion must be favourable for a trial to proceed (this opinion being part of a decision to grant authorization, one that could give rise to recourse, including recourse founded on the way in which an unfavourable opinion was given).

We have observed in the previous system notable weaknesses inherent in the difficult task of recruiting volunteers to participate in the meetings, in the fact that persons invited to join a CCPPBR were not well-informed about the Committee's structure and their potential role in it, and in the heterogeneity of the training of new members, all of which was reflected, in time, by a decline in attendance at meetings.

From one Committee to another, from one region to another, there are significant discrepancies in the number of dossiers submitted for opinion, the workload and heterogeneity in the evaluation process and the opinions given.

#### 2.4.2 Proposals

The Round Table group has proposed what the main elements should be to enable the harmonious operation of the CPPs. See table III.

### 3. Comments

The usual difference in interpretation between professionals in clinical trials and jurists with regard to the missions of the

Committees was observed in the course of the discussions, notably with regard to the meaning of the terms 'validity' and 'relevance' of the research project. Similarly, one might wonder about the involvement of the Committees in the evaluation of the qualifications of investigators, the suitability of the facilities for the research project and the satisfactory nature of the 'benefit/risk ratio' assessment for the research project. Legislators have arranged that the CPP and the administrative authority give their respective opinions in parallel. This raises the question as to whether the respective roles of each group lead them to do complementary work or cross-checking. At any rate, it appeared necessary for the exchanges between the competent authority and the Committee (exchanges that would in all probability be bilateral) to be organised, if only to reduce the timeframes for obtaining an opinion and an authorization as much as possible. There is effectively competition between Member States in terms of trying to attract sponsors of clinical research. These matters hinge, in particular, on the longer or shorter period of 'administrative time'.

For the participants of the Round Table, the introduction of the French system into this European competition seemed to require the implementation of new measures. These could be better financing of operating costs (i.e. premises, secretarial staff, equipment and archiving) as well as the allocation of a budget for personnel costs, including the possibility of paying external experts and reimbursing Committee members for expenses occasioned by their attendance at sittings, in particular transportation costs or even loss of earnings.

**Table III.** Implementation of harmonious operation of CPPs

#### **Harmonised operation common to all CPPs (fixed by decree/mandate)**

Internal regulations  
Procedures  
Provisions for a call for applications for members and for the formation of the group (medical/non-medical)  
Provisions for recourse to experts  
Training of members  
Audit and inspection  
Declaration of conflicts of interest  
Documentary and budgetary traceability  
Relations with the DGS, Afssaps, the DRASS  
Relations with patient associations and the public at large  
Indemnities for members and payment of experts

#### **Development of the network of CPPs**

Compulsory affiliation to the network (by decree?)  
Development of good practices and the principle of a quality approach  
Propositions for improvement of operation  
Computer assistance to encourage permanence of exchanges  
Case studies, training, etc.

From a structural point of view, the fact that the Committee has the status of a person under public law led us to emphasise the need for statutes, internal regulations and the writing of attainable standard operating procedures, against which compliance could be checked.

The presence of members of associations of patients and users of the healthcare system within the CPPs represents an important advantage in terms of the 'intelligibility of information' provided to the persons invited to participate in a research project.

Without going as far as affecting the independence of the Committees, it was hoped that a national coordinating body could be set up, with procedures designed to unify the operation and the reliability of the evaluation. This would be a structure for information and coordination, for the Committees themselves as well as for the members. Concerning the latter, the wish to see them informed and trained with regard to the objectives, responsibilities and operations of the Committee itself was expressed. In light of the fact that any possible conflicts of interest of members would have to be declared and updated on their behalf, it is to be hoped that provisions will be made for this declaration.

Finally, the members of the Round Table were in agreement about a proposal to establish a reference system by which the practices of the Committees could be assessed, in order to respond to the desire for excellence and promote professionalism and increase the stability of the Committees to preserve in the long term the experience that has been acquired.

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