

# Clinical Research Infrastructures and Networks in France: Report on the French ECRIN Workshop

## Infrastructures et réseaux de recherche clinique en France : le séminaire ECRIN

Jacques Demotes-Mainard,<sup>\*1</sup> Geneviève Chêne,<sup>\*\*2</sup> Christian Libersa<sup>\*3</sup> and Jean-Pierre Pignon<sup>\*\*4</sup>

\* Réseau des Centres d'Investigation Clinique ; INSERM-Hopitaux

\*\* Réseau Français des Unités d'Essais Cliniques ; Hôpitaux-INSERM-FNCLCC-Pasteur

1 Centre d'Investigation Clinique ; INSERM-CHU de Bordeaux, Bordeaux, France

2 Unité de Soutien Méthodologique à la Recherche Clinique, CHU de Bordeaux ; INSERM U-593 et Institut de Santé Publique, d'Epidémiologie et de Développement, Bordeaux, France

3 Centre d'Investigation Clinique ; INSERM-CHRU de Lille, Lille, France

4 Service de Biostatistiques et d'Epidémiologie, Institut Gustave Roussy, Villejuif, France

### Abstract

A meeting was organised in Paris on 13 September 2004, to provide an in-depth description of the state of the art in institutional clinical research infrastructures and their environment in France. This meeting was scheduled within the ECRIN (European Clinical Research Infrastructures Network) project, funded by the European Union (6th Framework Programme). Ten items were addressed: (i) centres and networks; (ii) funding and sponsoring of clinical research; (iii) ethics; (iv) legislation and regulation; (v) adverse-event reporting and drug dispensing; (vi) methodology, data management and data monitoring; (vii) quality management and audits; (viii) communication with investigators, sponsors and participants; (ix) transparency and registration of clinical studies; and (x) education and careers. This description, together with parallel workshops held in other countries using a similar pattern, helped prepare a comparative analysis enabling better identification of the bottlenecks for multinational research in Europe, and define the most relevant approaches to harmonisation and the services required to support the role of sponsors in transnational studies.

**Keywords:** clinical research, Clinical Research Centre, Clinical Trial Unit, network, sponsor, ethics, trial registry, regulation, training

### Résumé

Un séminaire organisé à Paris le 13 septembre 2004 a permis de procéder à une description approfondie de l'état des lieux concernant les infrastructures académiques de recherche clinique en France, leurs réseaux, ainsi que leur environnement. Ce séminaire était organisé dans le cadre du projet ECRIN (European Clinical Research Infrastructures Network) financé par l'Union Européenne (6<sup>e</sup> Programme-Cadre). L'analyse a porté sur dix points : (i) centres et réseaux de recherche clinique ; (ii) financement et promotion de la recherche clinique ; (iii) éthique ; (iv) législation et réglementation ; (v) gestion des effets indésirables et dispensation du médicament ; (vi) méthodologie, traitement et monitoring des données ; (vii) gestion de la qualité et audits ; (viii) communication avec les investigateurs, les promoteurs et les participants ; (ix) transparence et registres d'essais cliniques ; et (x) éducation et carrières. Des séminaires identiques ont été organisés dans chacun des pays participants afin de préparer une analyse comparée. En précisant les obstacles à la recherche clinique multinationale en Europe, cette analyse comparée permettra de définir quelles actions d'harmonisation mener

et quels services proposer aux promoteurs pour faciliter la réalisation d'études transnationales.

**Mots clés :** recherche clinique, Centre d'Investigation Clinique, Unité d'Essai Clinique, réseau, promotion, éthique, registres, réglementation, formation

A meeting was organised in Paris on 13 September 2004, to provide insight into the state of the art of the organisation, ethics and regulatory framework, as well as the environment of institutional clinical research in France. Two networks represent the French clinical research infrastructures in the European Clinical Research Infrastructures Network (ECRIN) programme, one more specifically concerned with the methodological conception and management of randomised clinical trials (the French Clinical Trial Units network [Réseau Français des Unités d'Essais Cliniques; RFUEC]), the other one focusing on experimental medicine, transnational research and the early steps in therapeutic evaluation (the INSERM [Institut National de la Santé et de la Recherche Médicale]-Hospitals CIC [Centre d'Investigation Clinique] network).

This meeting was the first step of the ECRIN programme,<sup>[1,2]</sup> consisting of national workshops designed to prepare a comparative analysis of ECRIN participating countries, to better identify the bottlenecks for harmonisation and transnational studies in academic centres in Europe: the objective of ECRIN is to connect national networks of Clinical Research Centres/Clinical Trials Units (CTU) in Europe in order to promote harmonisation of tools and practice, and to facilitate the conduct of transnational studies.<sup>[3]</sup>

In addition, this workshop raised further interest in the rapidly evolving picture of clinical research. As a result of the 2001/20/EC Directive<sup>[4]</sup> on clinical trials coming into force on May 2004, national implementation guidelines resulted in dramatic (and sometimes divergent) adaptations of pre-existing regulations, challenging the role of public sponsors. In France, the transposition of the 2001/20/EC Directive, the "Loi de Santé Publique" (9 August 2004), is awaiting implementation texts and comes into force during the first semester of 2005.<sup>[5]</sup> This new law covers any interventional clinical research (not only clinical trials), and brings some changes to the pioneering Huriet's law (1988). In addition, recent changes to the financial management of public hospitals at the national level will affect the financial management of hospital-based clinical research. Finally, constraints enforced by both previous and new regulations have been promoting the organisation and the professionalism of clinical research, fostering the development of both centres and networks of centres.

This report depicts the status of clinical research infrastructures in France in the current ethical, legislative and regulatory

context. Of course, this picture lacks exhaustiveness, and merely samples organisational elements illustrating the French specificity in clinical research.

## 1. Structures and Objectives of Centres and Networks

The two main actors in institutional research are the 29 University Hospital Groups (Centres Hospitaliers Universitaires [CHU], public institutions) and the 20 Cancer Institutes (Centre de Lutte Contre le Cancer [CLCC], private non-profit institutions). They comprise the majority of the institutional sponsors of investigators, CTUs (Unité d'Essais Cliniques [UEC]) and Clinical Research Centres (CIC). The Ministry of Health (Direction Générale de la Santé [DGS]), through the "Programme Hospitalier de Recherche Clinique" (PHRC) is the main source of public funding for clinical research. Charities and the pharmaceutical industry are the other two major partners funding institutional research. Two government agencies have a major role in structuring research: INSERM, devoted to both experimental and clinical biomedical research, and the "Agence Nationale de Recherches sur le Sida" (ANRS), devoted to AIDS and hepatitis. Other key actors are the cooperative groups of investigators, particularly in cancer, AIDS and cardiovascular diseases.

Two clinical research infrastructures networks are organised in France and participate in the ECRIN project, a CIC network consisting of hospital-based facilities devoted to experimental medicine and early steps in drug development, and a network of CTUs (UEC) with a background in methodology, biostatistics and data management, focusing on randomised trials and epidemiology (see Bell<sup>[6]</sup>). Collaboration between such structures is usual whenever studies require both types of services – clinical investigation or support to the investigator for the CIC, methodology, data management and data quality control for the UEC.

### 1.1 Centres

#### 1.1.1 The CICs (Centres d'Investigation Clinique)

In the early 1990s, the CIC INSERM-Hôpitaux were designed through a partnership between University Hospitals (CHU), steered by the Ministry of Health, and INSERM, a government research agency steered by the Ministry of Higher Education and Research. The objective was to provide investigators and sponsors with specialised facilities and professional teams

for the conduct of clinical research, especially transnational studies, in order to best implement the Good Clinical Practice (GCP) guidelines and the new regulation derived from the French legislation (Huriet's law, 1988). CICs are created on the basis of competitive calls and undergo competitive evaluation every fourth year, taking into account their scientific output, quality management, and financial viability. CICs also undergo systematic GCP audits.

CICs are designed as hospital-based facilities with specific personnel (practitioners, study nurses, research assistants and project managers, sometimes pharmacists and biostatisticians), and specific logistics (including beds and equipment). CICs act either as an investigator or as a support to investigators, providing a variety of flexible services (support for methodology, regulation, funding, conduct of the study) and also have the capacity to support investigators in various hospital departments, outside of its specific beds. Some CICs have developed biological resource facilities, and some have networks of corresponding practitioners able to foster enrolment and to conduct larger-scale studies.

CICs were more specifically designed as tools for transnational research (with specific links with INSERM experimental research laboratories) and experimental medicine, and are therefore best adapted to the early phases of drug registration. They also conduct strategy studies of marketed drugs (medicines trials as a whole represent about 50% of projects), pathophysiological studies (26%), genotype-phenotype (8%), diagnostic (7%), epidemiology (4%) surgery (4%) or medical device projects. Among these projects, 35% are monocentre studies, 36% French multicentre (especially through the CIC network), and 29% international multicentre studies (609 ongoing). Studies are performed in patients (74%), healthy volunteers (17%) or both (9%). Sponsors for the projects conducted in CICs are both industry sponsors (about 50%) and academic sponsors, mainly University Hospitals and INSERM.

The first centres were created from 1992, and subsequent calls led to the creation of 24 CICs up until 2004. Some of them specialise in selected medical fields, while others act as multidisciplinary infrastructures. Access to these infrastructures is provided through submission of the project to a Technical Committee, which pronounces on the scientific and methodological content of the project, and on its feasibility with regard to the CIC's logistics and compliance with GCP rules. Finally, CICs contribute to the training of investigators and clinical research personnel.

### **1.1.2 The UECs (*Unités d'Essais Cliniques*)**

Methodology units for clinical research were the first centres devoted to clinical research, some of them being created in the

1970s and 1980s. The Clinical Trial Units (UEC) are centres able to conduct randomised trials and correspond to the largest methodology units. Since the structuring, in the early 1990s, of public-sponsored clinical research stimulated by the availability of public funding (see 2.2.1), various institutions have developed UECs with the capacity to support public sponsors through their expertise in methodology, logistic organisation, data management, data monitoring, data analysis and quality control. They interact with investigators or investigators' networks in any medical field, and are housed in various institutions: universities, University Hospitals (CHU), cancer research and treatment centres (CLCC), scientific agencies (EPST [Etablissement Public à caractère Scientifique et Technique]): INSERM, ANRS, Pasteur Institutes. Some UECs focus on one domain like cancer, cardiovascular diseases or AIDS, but most of them work in several fields. They are funded by the institutions in which they are housed, and receive grants from public agencies and charities, and contracts with industry. They are evaluated through a scientific commission within their institution and through structure or study audits.

UECs participate in the professionalism in clinical research through their staff, mainly consisting of epidemiologists (usually medical doctors [MDs]), biostatisticians, data managers, computer scientists, project managers, study monitors (Attachés de Recherche Clinique [ARC]), quality managers. Services include support in the methodological design, in data analysis and interpretation, in the organisation of a study's conduct (randomisation, blinding, drug dispensation, data collection and monitoring, coordination of investigation sites), writing of scientific reports and publications. The UECs also participate in phase 1 and 2 trials, diagnostic evaluation, prognostic studies, genomic and pharmacogenomic studies, quality of life and cost evaluation, epidemiology, outcomes research, and meta-analysis. Beyond these services, UECs develop innovative methodologies and technologies best adapted to specific clinical research contexts. Finally, UECs also participate in methodology training of their own staff and of corresponding investigators.

## 1.2 Networks

### **1.2.1 The CIC Network**

The CIC network was initiated when the number of CICs reached critical mass in the early 2000s, and was officially created in April 2003. Its objectives are promoting collaboration and communication, optimising the quality and efficiency of research performed in CICs, and delineating shared research topics and strategies within the CIC network.

The network is steered by a board of six members, including a coordinator and two representatives of the INSERM administration. Meetings of the CIC network in the presence of the Director General of INSERM are organised every second month, allowing selected issues to be addressed by invited speakers. Working groups that communicate with the board and present the resulting activities at the network's meetings have also been initiated. Working groups currently cover harmonisation of cost evaluation and financial management; harmonisation of standard operating procedures (SOPs); development of shared information systems; and development of a collaborative website. Further working groups are expected to start in 2005: transnational research/links with experimental research laboratories, development of partnerships, connection with European networks, and further development of topic-specific subnetworks (cardiovascular diseases, neurosciences, paediatrics). Finally, the network promotes the conduct of multicentre clinical studies within the network (currently more than 20 studies, two-thirds pathophysiology, one-third therapeutic), and this was stimulated by a specific call launched by INSERM to fund projects carried out within the network.

In total, the network has 95 hospital beds, and its staff includes 101 MDs or pharmacists, 69 study nurses, 51 clinical research (Technicien de Recherche Clinique [TRC] or Assistants de recherche clinique [ARC]) and administrative personnel, 27 biostatisticians, psychologists or senior scientists.

### **1.2.2 The UEC Network (RFUEC (Réseau Français Des Unités d'Essais Cliniques))**

The UEC network was created in October 2002 to facilitate national and European collaboration, with an administrative affiliation to ISPED (Institut de Santé Publique, d'Epidémiologie et de Développement Bordeaux-2 University). Members (currently 38) are UEC housed in public institutions (some of them – FNCLCC, AP-HP [Fédération Nationale des Centres de Lutte Contre le Cancer, Assistance Publique-Hôpitaux de Paris] – having multiple UECs). Five are INSERM units, ten cancer institutes (CLCC) units, two Institut Pasteur units and the remaining are CHU units. UECs are coordinated by a methodologist, and carry out randomised trials in any medical field. The network covers a large spectrum of disease, and its multidisciplinary nature is associated with a high degree of national and international multicentre activity in clinical trials outside of the scope of the industry, and also with diagnostic or prognostic studies. In 2003, the network staff included 58 project managers, 65 biostatisticians, 24 computer scientists, 64 data managers.

The network is steered by a 6-member board, whose objectives consist of achieving a high standard of quality in institutional trials through expertise, training and harmonisation. The

network meets twice a year, and working groups are in charge of the following: (i) shared SOPs; (ii) common quality standards (accreditation, peer-review, data quality control); (iii) data management tools, skills and practice; (iv) training and teaching; (v) collaboration in national trials, in particular in decentralised monitoring; and (vi) connections with European networks. The network also releases a list of methodologists with specific skills, enabling the selection of experts for reviewing protocols or for independent data-monitoring committees, and promotes training sessions for various "actors" in clinical research, including those involved in the implementation of the European Union (EU) 2001/20/EC Directive.

## **1.3 Partners in the Structuring of Clinical Research Infrastructures**

### **1.3.1 Ministry of Health and University Hospitals**

In November 1992, the Ministry of Health decided to assign specific funding for clinical research (PHRC, see 2.2.1) and to set up within the University Hospitals (CHU) an office in charge of the management of these projects, the "Délégation à la Recherche Clinique" (DRC). This was the first involvement of hospitals as actors in clinical research, both at the institutional and national levels (formerly, investigators collaborated directly with sponsors without contact with the hospital). This allowed hospitals to conduct clinical research with a specific management system (scientific, regulatory, quality and financial management), acting either as a sponsor, or in partnership with other public or industry sponsors. This system also allowed hospitals to act as partners, through their DRC, in the organisation and the management of CICs.

More recently, DRCs have focused on their networking and on the development of topic-specific facilities (i.e. bioterapy), biological resource facilities, data monitoring, and scientific evaluation. This has led most CHUs to create their own CTUs (see 1.1), with their financial support being mainly dependent on their institution.

CHUs also participate in the financial support of CICs; however, funding of clinical research through public hospitals is currently poorly harmonised in France. Financial support to CICs varies from one CHU to another (apart from an initial grant provided by the Ministry of Health [Direction de l'Hospitalisation et de l'Offre de Soins; DHOS] during the first 4 years, €46 000/year). However, a working group (CIC network and the "Fédération Hospitalière de France" [FHF], which coordinates activities in public hospitals) with the aim of harmonising cost evaluation in CICs led to the proposal of common guidelines.

Moreover, a dramatic change in the financial management of public hospitals (Tarification à l'Activité [T2A]) has been implemented from January 2005. Previously, the annual budget assigned to each hospital, and to each department within the hospital, was not strictly dependent on the healthcare activity. This 'Global Budget' system will be replaced by an accounting system based on the amount of care produced by each department. However, additional funding (probably up to 13%) can be assigned for activities not directly related to care (Missions d'Intérêt Général [MIG]), including teaching and research activities. For every hospital, the amount of such support will be determined as a function of indicators, including research output, sponsorship activity, and the presence of research infrastructures (CICs, CTUs, research laboratories). How this support will be calculated, and how this money will be distributed within the hospital is currently a matter of debate; however, it could be expected that this reform will result in a better harmonisation in the financial support of clinical research infrastructures by hospitals.

### 1.3.2 Government Scientific Agencies

Among government scientific agencies (EPST), only INSERM is exclusively devoted to biomedical research, covering both the experimental and clinical fields. Regarding clinical research, its activities consist of the following:

- *Supporting infrastructures through a partnership with hospitals:* CICs, and more recently specialised facilities (Biotherapy, Epidemiology), corresponding to a total investment of €2 million/year), and biological resource facilities (€5.6 million over 3 years). The role of INSERM in the activity of CICs is complementary to the role of hospitals. INSERM stimulates translational research through links with experimental research, and organises at the national level both scientific activities (topic-specific networks in neuroscience, cardiovascular diseases, paediatrics) and structuring activities (working groups promoting harmonisation and facilitating collaboration between CICs). A specific call for projects funds multicentre clinical research performed within the network (see 1.2 and 2.2.1).
- *Acting as an academic sponsor (see 2.1.3):* Other EPSTs also act as sponsors in selected fields: the INRA (Institut National de la Recherche Agronomique) for nutrition research, the CNRS (Centre National de la Recherche Scientifique) and the CEA (Commissariat à l'Énergie Atomique) for cognitive science, imaging, and health technology projects.
- Career opportunities, allowing for mobility between basic and clinical research.
- Coordinating its action with various partners (hospitals and universities) for a better synergism at the local level. In ad-

dition, contracts with universities will be designed in order to support clinical research projects (Plan Pluri-Formation [PPF]).

### 1.3.3 Charities and Foundations

The involvement of charities and foundations in the organisation of clinical research in France is best illustrated by the 20 cancer research and treatment institutes (CLCC). Teams of clinical research technicians (TRC) mainly involved in the sponsors' tasks and in providing support for investigators were developed within the CLCC network, under the umbrella of a National Federation (FNCLCC). Many of these teams are supported by a CTU for data management and biostatistics. Ten of the 20 cancer institutes have their own CTU, which is a member of the UEC network. At the national level, the Office for Clinical and Therapeutic Studies (Bureau d'Études Cliniques et Thérapeutiques [BECT]) of the FNCLCC has itself developed the capacity to act as a sponsor in oncology trials, particularly in rare disease/orphan drug studies, keeping close contacts with patients' associations. The BECT acts as a support (shared SOPs, regulatory affairs, funding opportunities) for CLCCs, which perform 72% of public-sponsored studies.

### 1.3.4 Universities

The role of universities in clinical research is less developed in France than in countries where University Hospitals are steered by the university. Universities are not always involved in CICs, created on the basis of a partnership between INSERM and hospitals, even though some of their personnel are employed by the university. On the other hand, a subset of CTUs are housed in, and supported by, universities. In this context, a partnership between universities and scientific agencies will be developed to support teams conducting clinical research projects (PPF, see 1.3.2). Altogether, the influence of the university remains low in the organisation of clinical research centres, and in turn their role as partners in training is underexploited by universities.

### 1.3.5 Industry

Pharmaceutical companies played a role in the early organisation of clinical research centres (CIC), with the objective of providing hospitals with the skills necessary for conducting high-quality clinical research. In 1992, a contract between the pharmaceutical company Merck and INSERM fostered the first call for the creation of CICs, providing financial support to both the infrastructures and projects carried out within the centres. In return, the industry had a "priority" access to the infrastructure. Several UECs have long-term collaboration with the industry in conducting clinical trials, reviewing industrial trials, and training research staff.

## 2. Partners in Projects: Financing, Sponsoring

### 2.1 Sponsorship

Since Huriet's Law (1988), regulation, liability and administrative burden have made the role of investigators-sponsors very difficult in France. Therefore, various public institutions have developed the capacity to act as public sponsors in order to maintain a capacity to perform clinical research.

#### 2.1.1 Industry

In France, 70% of the clinical research on medicinal products is industry sponsored, while 30% is sponsored by institutions. From the industry point of view (survey by LEEM [Les Entreprises du Médicament]), the attractiveness of France is considered intermediate in terms of objective criteria (% of active centres, number of patients per centre, enrolment rate). In turn, attractiveness is viewed as poor when more subjective criteria are used: productivity, quality of investigators. The quality of the French health system and of regulatory authorities is positively perceived, as well as the single opinion in ethical review (however, this advantage of the French system will disappear with the implementation of the 2001/20/EC directive).

#### 2.1.2 Hospitals

As a consequence of the implementation of the first French legislation on clinical research (Huriet's law) in the early 1990s hospitals developed offices (DRC, see 1.3.1) whose primary objective was to act as a public sponsor, with the ability to cover financial management, quality control and medical liability in clinical research projects. This function was devoted to hospitals rather than to universities, as patients, investigators, and biological material are present in hospitals.

Public funding for clinical research from the Ministry of Health (PHRC, see 2.2.1) strongly enhanced this role of University Hospitals (CHU) as public sponsors: currently, about 1000 clinical research projects are sponsored by the 29 CHUs, with a significant number of multicentre projects.

Later, audits from Competent Authorities, identifying deficiencies in quality control, data management or drug dispensation, stimulated the development of additional activities leading to a set of services available within the DRCs: methodological support (through CTU), data management, financial management, pharmacovigilance and drug dispensation, clinical investigation, and data monitoring. With regard to data monitoring, some DRCs use an approach based on the stratification of monitoring into four standards as a function of the risk associated with the study (see 6.6).

#### 2.1.3 Scientific Agencies/Scientific Associations/Foundations

Among government scientific agencies (EPST), INSERM is the main public sponsor for clinical research projects, whereas ANRS acts as a sponsor specifically in AIDS and hepatitis (CNRS, CEA and INRA also act as sponsors in selected fields).

INSERM currently sponsors 110 projects, and about 40 new projects per year. This activity is complementary to the hospital sponsorship, and it deals mainly with translational research on innovative diagnostic or therapeutic tools originating from experimental medical research, and with proof-of-concept studies in humans. Genotype-phenotype and pathophysiological studies represent 80% of INSERM-sponsored research. This sponsorship activity is supported by specific services (methodology and data management, data monitoring, drug dispensation and pharmacovigilance). Sponsorship is obtained after projects are evaluated by a board (Comité d'Orientation Stratégique et de Suivi des Essais Cliniques [COSSEC]), while a clinical research office supports experimental and clinical researchers in the organisation of clinical studies. Finally, CICs play a pivotal role in the implementation of these transnational research activities.

ANRS is a disease-specific agency based on a partnership between various ministries and scientific agencies, including INSERM. ANRS organises and funds research on AIDS and hepatitis, with 40% of its budget (total €43 million) devoted to clinical studies. ANRS currently sponsors 30 trials and 15 cohorts, with a yearly turnover of ten projects. ANRS acts through the following: (i) a clinical research department in charge of regulatory affairs, financial management, GCP and pharmacovigilance; (ii) six methodology and data management facilities (including five from the UEC network); and (iii) a nation-wide network of investigators, and virology, immunology and pharmacology laboratories. ANRS also acts in developing countries.

Few scientific associations have the capacity to act as a sponsor (with the exception of well-organised fields such as haematological oncology), and charities provide funding, not sponsorship.

Regarding the cancer institutes, as previously stated (see 1.3.3), FNCLCC has developed, through the BECT, the capacity to act as a sponsor at the national level. At the regional level, several cancer institutes can also act as sponsors and provide services similarly to the DRC.

## 2.2 Funding of Research Projects

The income of clinical research centres (CIC and UEC) is partly based on an annual grant assigned to the infrastructure by INSERM (€46 000/year for CIC), by hospitals and the Ministry of Health (variable amount), and other partners such as the Ministry of Universities and Research, charities, and the industry.

However, most of the income of clinical research infrastructures is derived from projects carried out within centres: industry-sponsored projects, or public-sponsored projects. These centres receive part of their financial support from the industry; however, public funding is critical for their independence from the industry and the scientific activity of centres.

A survey carried out in 2003 by the Ministry of Universities and Research evaluated the resources for clinical research in France at about €100 million in the year 2000, including extra costs for industry-sponsored projects (€16.6 million) [however, salaries for tenured staff are not taken into account in this evaluation]. No data were given regarding the part corresponding to research carried out in CICs and UECs.

### 2.2.1 Public Funding

The main source of public funding for clinical research projects in France is derived from the Ministry of Health (DHOS), through the PHRC, which was initiated in 1993 with the objective of stimulating clinical research in hospitals. Funding of clinical research projects currently represents €40–45 million/year, and project evaluation is carried out both at the national and the regional levels:

- the national call (60% of funding, about 110 projects per year, mean funding €250 000) covers multicentre projects on topics selected annually;
- the regional calls (40% of funding, about 240 projects per year, mean funding €70 000) cover smaller projects in any field (except AIDS and hepatitis, covered by ANRS).

Other main public funding opportunities for clinical research projects include the following:

- scientific agencies: for instance, INSERM provides funding for clinical research projects on selected topics or for multicentre projects carried out within the CIC network (see 1.2 and 1.3.2); on the other hand, ANRS specifically supports clinical research projects on AIDS and hepatitis (see 2.1.3). INRA funds nutrition research, and CNRS supports clinical research in various fields, including genetics, imaging and cognitive science;
- funding from the Ministry of Universities and Research, the Ministry of Industry for the clinical development of innovative tools;
- funding may also be obtained from other public sources, including the public medical insurance system (Caisse Régionale d'Assurance Maladie [CRAM]) for projects on prevention;
- some hospitals have developed internal grants aimed at supporting a restricted number of pilot studies (about €15 000 per project).

Typically, funding of clinical research projects covers salaries and operating expenses, not those for the equipment. Additional public funding may be obtained for equipment related to clinical research projects through grants developed in some regions (Conseil Régional), by scientific agencies or ministries, contributing to both the conduct of projects and the structuring of clinical research centres.

### 2.2.2 Charity Funding, Foundations

Support of clinical research by charities is illustrated by the activities of the “Ligue Nationale Contre le Cancer”, which spends €3.4 million/year in funding clinical research projects on the basis of specific calls, but also through support to the Cancer Institutes network (FNCLCC, see 1.3.3 and 2.1.3), and through a grant for clinical research teams. Funding is available for operating expenses as well as for equipment.

A large number of other charities and foundations contribute to the financial support of clinical research in France, including the AFM (Association Française contre les Myopathies), which manages funds collected by Telethon and supports both experimental and clinical research on genetic and rare diseases.

### 2.2.3 Scientific Associations

As previously stated, sponsorship by scientific associations is quite uncommon in France. They rather provide logistical or financial support to clinical research projects, as well as salaries for young researchers for a specific project.

## 3. Ethics

The former (Huriet's law, 1988) French legislation covering interventional studies resulted in a variety of national characteristics that will be moderated by the new legislation implementing the EU 2001/20/EC Directive. In particular, the previous distinction between research with (ABID [avec bénéfice individuel direct]) or without (SBID [sans bénéfice individuel direct]) ‘direct individual benefit’ is abandoned and replaced by an evaluation of the risk-to-benefit ratio. According to Huriet's law, this classification influenced the following: insurance status; the possibility of compensation (only for SBID) for participating subjects with an annual maximum income of €3000, registration of subjects on a national volunteers' file; the possibility of subjects participating simultaneously in two studies; the exclusion periods; and the requirement to investigate subjects in a previously authorised environment (“autorisation de lieu”). Such a distinction between SBID and ABID research is now replaced by an evaluation, performed by the committee, of the risk-to-benefit ratio.

Ethical review will be performed by “Comités de Protection des Personnes” (CPP, instead of the former “Comités Consultatifs de Protection des Personnes dans la Recherche Biomédicale” [CCPPRB]). Although independent, their status, rules and composition are defined by the regulations, and members are appointed by the regional representative of the State. The State is responsible in the case of misconduct. Moreover, when the Committee makes a negative decision on a project, the sponsor may appeal to the Ministry of Health, who can ask a second CPP to give its opinion. The law now states that among the members of the CPP should be included representatives of patients’ (or health system users’) associations. The number of CPPs is expected to remain constant (about 50), organised on a regional basis.

The single opinion doesn’t represent a change, as this procedure was already the rule in the previous law: a CPP located in the region of the coordinating investigator will be asked to provide an authorisation valid for the whole country. Contrary to the previous procedure, it will be contacted by the sponsor instead of the investigator. Moreover, information will be exchanged with the “Competent Authority” throughout the study.

In the former system, fees for submission to CCPPRBs were €1450 or €145 for industry or public sponsors, respectively, and the opinion was available within 5 weeks – this interval is not expected to increase.

CPPs will be asked to give an opinion, not only on clinical trials but also on any interventional study as defined by the law of August 9, 2004 (see 4.1). Observational studies and studies evaluating usual care are not considered (however, under borderline conditions corresponding to studies evaluating usual care, but with the addition of follow-up procedures specific to the study, investigators will be asked to collect the opinion of a CPP and the informed consent of patients, without the requirement for a sponsor or an insurance).

When the participant lacks the capacity to give written informed consent, a third person independent from both investigator and sponsor should testify on behalf of the subject. Under emergency conditions and when stated in the protocol approved by the CPP, this third person could be replaced by a family member or a trustworthy person (“personne de confiance”). A set of specific procedures also apply to children, protected persons or persons unable to give informed consent (although the waiver of consent in critically ill patients was not considered in the 2001/20/EC Directive, thus making clinical research under emergency conditions possible in France).

As a function of risks and constraints associated with the study, the CPP also states on whether or not the subjects should receive compensation for their participation in the study (exclud-

ing children, vulnerable and protected populations), and decides the amount of this compensation (an annual cumulative upper limit will be given by implementation texts). The CPP also decides whether it is possible for subjects to participate simultaneously in another study and, when relevant, on the duration of an exclusion period after completion of the study. In such cases, subjects must be registered on a national volunteers’ file, allowing control of the maximal annual compensation and the exclusion period.

It will also pronounce on the fitness of the medical environment to the investigation. Whenever research involves an investigation different from the usual care in this environment, a previous site agreement (“autorisation de lieu”) should be obtained from the regional health authority (Direction Régionale des Affaires Sanitaires et Sociales [DRASS]). The CPP can also ask for an independent data monitoring committee.

Improvement in transparency represents another ethical characteristic of the new French legislation: the subject information sheet should now include data on alternative therapeutic strategies, and on the nature of care provided after completion of (or exclusion from) the trial; registration of clinical trials in an open, EudraCT-derived database could be requested unless there is a justified refusal by the sponsor; subjects participating in clinical research will have access to the data relevant to their own medical status, and will be kept informed of the global outcome of the study, if they so wish it (see 9.1). The procedure for providing the subject with such information will be described on the informed consent sheet.

#### 4. Legislation, Regulatory Affairs, Good Clinical Practice (GCP), Insurance

##### 4.1 Legislation

The transposition of the 2001/20/EC Directive, the “Loi de Santé Publique” (9 August 2004<sup>[5]</sup>), is awaiting implementation texts and will enter into force during the first semester of 2005. This new law covers any interventional clinical research (not only clinical trials), and brings some changes to the former Huriet’s law (1988).

As did the Huriet’s law, this new law applies to any clinical research protocol different from observational studies (epidemiology, pharmacoepidemiology, evaluation of usual care, in which every investigational, diagnostic, therapeutic or follow-up procedure strictly correspond to usual practice). As stated in section 3, however, studies evaluating usual care and with the only addition of specific follow-up procedures are not covered by the law, but



require only the agreement of the CPP and the informed consent of the patient.

Patients and subjects enrolled in clinical studies should undergo a medical examination, and be covered by the public medical insurance system (Sécurité Sociale). One major change brought to the former law is the deletion of the distinction between ABID and SBID clinical research (see section 3).

The role of the sponsor extends beyond the requirement of the EU Directive, as it applies to any interventional study. This sponsor should be housed in the EU, or act through a legal representative housed in the EU. The investigator is defined as a competent professional, usually an MD (however, in some research other health professionals may act as investigators). In turn, some of the previous investigator's tasks are now assigned to the sponsor (particularly the communication with the CPP).

Any clinical research covered by the law is expected to observe a procedure derived from that described in the 2001/20/EC Directive, consisting of a parallel submission of the project with a dossier, including an investigator's brochure (when relevant), by the sponsor to the Ethics Committee (CPP) and the regulatory authority. The sponsor should also ask for authorisation from both organisations for any substantial amendments, declare adverse reactions (7 days for serious, 15 days for other) and new facts affecting the risk-to-benefit ratio, as well as provide an annual security report. In France, two organisations, both dependent on the Ministry of Health, act as Competent Authorities: Afssaps (Agence française de sécurité sanitaire des produits de santé) for therapeutic studies on health products (medicinal products, medical devices, biotherapy); and the DGS for other treatments (surgery, radiotherapy), pathophysiological, genotype-phenotype studies and biological resource facilities. The opinion of the CPP and that of the Competent Authorities are expected to be provided within less than 60 days, and implementation texts will shorten this duration (see 4.2). In addition, clinical trials will follow the EU regulation: declaration on the EudraCT database, and use of the EudraVigilance system (see 5.1). More generally, adverse reactions should be declared both to the CPP and the Competent Authority following a specific procedure for each type of biomedical research (see 5.1).

#### 4.2 Regulation and GCP: Implementation Texts on Trials on Health Products

Implementation texts on therapeutic biomedical research, declared to Afssaps as a Competent Authority (medicinal products, medical devices, biotherapy), will enter into force during the first semester of 2005. However, Afssaps has organised a pilot phase,<sup>[7]</sup> during which assessment of the clinical trial is provided

within 30 days, 60 if additional information is needed. For phase I studies, these intervals are 14 and 30 days, respectively (except for biotherapy: 90 days). Whenever the drug under study is already marketed, or is already authorised for use in clinical trials, a simplified procedure will be used, with a shortened evaluation period (14 days). Implementation texts are also expected to synchronise the evaluation periods for CPP and Afssaps, to clarify their respective roles in authorising biomedical research and the procedures for exchange of information during the evaluation and throughout the study.

The national volunteer's file is managed by the Competent Authority (see section 3). For institutional sponsors, the principles of GCP protecting subjects and data quality will be applicable; however, possible adaptation depending on the characteristics of the trial and the investigational products can be considered (including by means of a risk-based modulation of data monitoring, see 6.5). The content of the clinical trial's authorisation dossier, particularly the investigator's brochure for marketed drugs will be further defined, and the possibility of sponsors being exempt from providing marketed drugs in strategy studies is under discussion.

#### 4.3 Other Studies, Biological Resource Facilities, Genetics, Pathophysiological Studies

The DGS is the Competent Authority for biomedical research other than studies on health products, which means that these studies should be submitted to the DGS by the sponsor, be covered by insurance, and receive parallel authorisation from the CPP and the DGS before initiation. A special reference should be made to collection of biological material: in any case, this must be declared to the Ministry of Research and to the CPP, with an appropriate informed consent procedure, relevant scientific justifications and ethical context. The CPP will also decide on the validity of the initial consent when a change is made to the scientific objective of the collection. The legislative status and the declaration to the competent authorities depend on the nature of the collection: whenever a collection of biological material is performed within a hospital during usual care, it observes the August 6, 2004 law on Bioethics and should be declared to the DGS and to the regional health authority (Agence Régionale de l'Hospitalisation [ARH]), but is not subject to the law on Biomedical Research (Loi de Santé Publique [9 August 2004]<sup>[5]</sup>). In turn, any collection carried out with research objectives is covered by the Loi de Santé Publique (9 August 2004<sup>[5]</sup>), and thus requires a sponsor, insurance, and must be declared to the relevant Competent Authority (DGS and/or Afssaps).

#### 4.4 Insurance

Since 1988 (Huriet's law), the civil and criminal liability for clinical studies in France has been assigned to the sponsor. Any interventional clinical research study thus requires insurance covering the sponsor (however, investigators are encouraged to obtain personal insurance as the sponsor's insurance company could take action against them). Beginning in 2005, the insurance system will be simplified in accordance with the new legislation (9 August 2004<sup>[5]</sup>). Under the new regimen, similarly to the former ABID procedure, the sponsor's liability is restricted to cases of presumed misconduct (i.e. any damage related to the study, even though no misconduct is demonstrated). This means that the sponsor is liable unless it can show the damage is unrelated to the study (demonstrating the absence of misconduct is almost impossible). In other cases, subjects are covered by a national compensation fund (Office National d'Indemnisation des Affections Intégrées et des Infections Nosocomiales [ONIAM]) created in 2002 (Kouchner's law).

Insurance coverage will last for a maximum of 10 years after completion of the study (instead of 30 years between 2002 and 2005, 10 years before 2002). Minimal (and usually maximal) compensation is €0.76 million per subject, €4.6 million per study, €7.6 million/year per sponsor, and the standard cost of insurance for a public sponsor ranges between €1000–2000 per study.

### 5. Adverse-Event Reporting, Drug Dispensing

#### 5.1 Adverse-Event Reporting

The European 2001/20/EC Directive, in parallel with the International Conference on Harmonisation (ICH) guidelines, has resulted in better harmonisation in the management of adverse events, at least in medicines trials. In France, the new procedure defined by the 9 August 2004 law<sup>[5]</sup> covers every interventional study, not only medicines trials: generally speaking, the investigator must declare adverse events and effects to the sponsor, then the sponsor must report them to both the Competent Authority (Afssaps or the DGS) and the CPP, and forward this information to every investigator. When the risk is altered, the CPP must make sure that the participants are informed, and that their consent to further participate is collected (however, CPPs do not have access to EudraVigilance).

Regarding medicines trials, France will implement the EU rules: definition of expected events in the protocol with the help of the investigator's brochure, declaration of suspected unexpected serious adverse reaction (SUSAR) on the EudraVigilance database by the sponsor, as well as a report of any new fact. The

sponsor will be asked to provide an annual safety report stating any changes in the risk-to-benefit ratio, to both Afssaps and the CPP, possibly leading to amendments. This results in a need for training and a substantial burden for public sponsors (Medical Dictionary for Regulatory Activities [MeDRA] coding, management of the EudraVigilance database, software), leading to increased complexity and professionalism in the sponsor's tasks.

Although without the centralised EudraVigilance system, similar rules (parallel notification by the sponsor to the CPP and Competent Authority, new facts and annual report) will be observed in France for other types of biomedical research covered by the new legislation. This includes the immediate notification of serious events (unexpected, and expected?) occurring during trials of medical devices and biomaterials, or related to clinical investigation in genotype-phenotype or pathophysiology studies. However, implementation texts will further define the declaration procedure.

Finally, adverse events occurring in observational studies on health products not covered by the 9 August 2004 law<sup>[5]</sup> (epidemiology, pharmacoepidemiology, evaluation of usual care) require declaration to the regional pharmacovigilance centre, according to the usual pharmacovigilance system.

#### 5.2 Drug Dispensing

An investigational medicinal product (IMP) is defined in Europe in article 2 d) of directive 2001/20/EC and in France in article L.5121-1-1 of the French public health code. However, the definition of the IMP still lacks harmonisation in Europe.

In France, the role of the hospital pharmacy is pivotal in IMP traceability and safety, and specific regulations describe the IMP cycle (specific regulations also exist for bioterapy products).

According to article L.5126-5 of the French public health code, a pharmacy in a hospital or a health centre can manage, supply, prepare, control, store and dispense an IMP.

For trials of medicinal products performed in hospitals or health centres, the pharmacist must be informed by the sponsor, together with the director of this institution. The pharmacist then checks information relating to the IMPs and the trial (including the investigator's brochure), checks and agrees on administrative documents related to the tasks of the pharmacist during the trial (protocol, financial contract with the institution). His task also consists of receiving the IMP, inspecting the parcel upon its arrival, and reporting any significant discrepancy observed: Is the parcel opened, damaged, or have its contents been stolen? Does it contain the expected products? Are they in good condition (i.e. temperature whenever the product requires shipment under refrigerated conditions)?

The IMPs are required to be labelled with a specific labelling according to the provisions of article R.5121-16 or GMP principles and guideline 12, item 18, as anticipated by the Order of May 10, 1995, modified.

For example, article R.5121-16 specifies the following particulars: name and address of the sponsor, trial reference code, reference of the IMP, batch number, expiry date, the storage conditions, and the statement “*utilisation sous stricte surveillance médicale (art R.5121-16 du code la santé publique)*”.

The pharmacist is responsible for the correct labelling, and storage and dispatch of the IMPs; he also ensures their traceability and that there is an inventory of the different IMPs. During the conduct of the trial, he is in charge of counting and storing the unused IMPs (this can be delegated to the investigator). After completion of the trial, he destroys the remaining unused IMPs after the sponsor’s authorisation (or returns them for destruction to an agreed authorised site).

Current French law states that the pharmacy where the IMP is purchased, packaged and labelled must be authorised by the regional health authority (ARH).

Public sponsors may be required to manufacture, import, re-release, package and label the IMPs. According to article L.5124-1 of the French public health code, these operations must be carried out in pharmaceutical establishments regularly authorised for these operations by Afssaps, observing GMP standards, and have a qualified person in charge. Also, according to article L.5126-11 and R.5126-9 of the same code, a legally authorised pharmacy in a hospital or health centre can carry out the preparations for a clinical trial.

In multicentre hospital trials, the pharmacist can ship IMPs to the other hospitals where the trial is conducted, when a specific authorisation is obtained from Afssaps (according to article L.5126-1).

The authorisation request specifies in particular the rationale of the trial, the protocol, the address of the sponsor, the location of the trial, the name of investigators, the number of subjects, the name and origin of the IMP, the name and address of the pharmacist, the tasks assigned to the pharmacist, the logistics, and the list of other hospital pharmacies involved.

## 6. Methodology, Data Management, Data Quality Control

### 6.1 Methodology/Biostatistics

French CTUs aim at covering the whole spectrum of the biostatistical support for clinical studies, from conception to publication. The network considers that a clinical research project

should include a methodologist (epidemiologist/biostatistician) from the very beginning to the end of the study to reach high-quality standards. Its specific activities are as follows: identification of an efficient study design, assistance in drafting the protocol and the case-report form (CRF), organising data monitoring, data management and data analysis, assistance in drafting the study report and scientific publication. At each step, the methodologist guarantees the conformity to national laws and quality standards. The CTU network is currently working on a description of the biostatistical tasks allowing a high-quality service to be attained – and this could be proposed as a basis for audit/accreditation of centres in the European network.

### 6.2 Tools and GCP in Data Storage

Data storage includes different activities: CRF storage, database storage. The recommended duration for the CRF and storage of essential trial documents is 15 years after the end of the trial, except when the trial is dedicated to a Marketing Authorisation. There is currently no common policy regarding data management tools and standards within the CIC or the UEC networks. However, working groups were recently set up in both networks to address this issue. The fragmentation of practice regarding data management is reflected in the variability of practices, depending on the sponsor and on the research centre. Only some tools (eg. ClinInfo, Macro) available in France allow for systematic implementation of specific SOPs according to ICH recommendations.

### 6.3 Regulations on Data Storage: CCTIRS and CNIL

Since 1978, three laws define the French regulations regarding data protection and access for each patient to his/her personal data and to the overall results of the study. Clinical research projects must therefore be submitted to two committees, the CCTIRS (Comité Consultatif pour le Traitement de l’Information sur la Recherche en Santé) for the content, and then the CNIL (Commission Nationale Informatique et Libertés) for the format.

A first principle deals with the content, specifically for data on health or disease and therefore clinical research projects, stating that every project must be declared to the CCTIRS. This committee examines the scientific basis for data collection (especially for data on genetics, ethnicity, political and religious opinion), the adequacy of the CRF (no more data recorded than required by the objectives of the project) and the conformity of the information given to the subjects on the protocol (all major data are described in the subject’s information form). Response is expected within 1 month.

A second principle deals with the format, stating that all databases containing information allowing direct or indirect identification of a subject should be declared to a National Committee, the CNIL, through a specific document. The CNIL considers that a database complies with the law if it guarantees its security (e.g., limited access with specific authorisations), if subjects are informed that their data are stored in a computerised database, that they have free access to these data, and the capacity to correct them. Authorisation is provided within 2 months, but a simplified yearly declaration procedure exists for centres managing data from multiple studies.

#### 6.4 Centralised Databases as Tools for Meta-Analyses

Centralised databases provide researchers with an efficient collaborative tool, aiming at improving the quality of data recorded and the power of analyses in clinical research projects. Several teams in France have the experience of leading such collaborative research in several fields: cancer, hepatology, HIV, and cardiovascular diseases. Although no specific academic support is given to such collaborative initiatives, centralised databases were recognised as very efficient tools for clinical research in Europe.

#### 6.5 Quality Control and Monitoring

Quality control and data monitoring are the sponsor's responsibility. Although differences exist between public sponsors, some of them have developed, following the Paris Hospitals' (AP-HP) initiative, the capacity to implement EU directives pending an adaptation of the monitoring standard as a function of the risk associated with the study. Four levels of risk are defined: 1 = minimal; 2 = low, similar to the risk in usual care; 3 = high; 4 = maximal. For example, the risk is minimal in an epidemiological survey with collection of a blood sample, and the risk is maximal in a phase I trial, a study in intensive care or a gene-therapy trial. Depending on this risk, monitoring will target all data in every patient (maximal risk), some critical data in every patient (high risk), or critical data in some patients (low risk). This procedure is currently implemented by some public sponsors, including the AP-HP and INSERM.

In their capacity of providing support to sponsors, the French CTU network is developing guidelines for data-monitoring procedures in order to harmonise practice in France. The network is also considering cost-effective procedures for quality control and monitoring in institutional research, with the aim of decreasing costs, not quality, and evaluation of such methods will be needed.

## 7. Quality Management, Standard Operating Procedures (SOPs), Audits

### 7.1 GCP Audits of Clinical Research Infrastructures

Study and structure audits of public clinical research infrastructures are becoming increasingly common. They are performed according to French legislation and regulations, GCP rules derived from the ICH, and French guidelines on GCP (1987).

Study auditing is common in industry-sponsored projects; however, some study audits were performed in public-sponsored projects, upon request by the Competent Authority, with increasing frequency. This resulted in a substantial improvement in the structuring of academic sponsors.

Systematic structure audits are performed within the CIC network, specifically to control the set of SOPs, its implementation, and the auditing of two randomly selected studies. The UEC network is working on definition criteria for CTUs (tasks, tools, practice) in order to allow for harmonised auditing specifications.

### 7.2 Working Groups on Quality Management and SOPs

Both the CIC and the UEC networks have developed working groups on quality management and SOPs. This allows the development of shared SOPs, promoting harmonisation within the network and facilitating the conduct of multicentre studies. Such working groups are open to a Europe-wide extension.

## 8. Communication/Partnerships

### 8.1 External Communication on Clinical Research

Recent advances in ethical, legislative and regulatory aspects, growing expectations for information and transparency from the general population, and the need to inform patients and patients' associations on clinical research led to the development of information policies, together with information on possible partners (industry, sponsors, funding agencies) in clinical research infrastructures. Groups working on cancer and AIDS research have collaborated with patients for several years. For instance, the "Ligue Nationale Contre le Cancer", in collaboration with FNCLCC, has organised various programmes for the patients: yearly national meeting for patients and their relatives, brochures on different cancers, participation of patients in the preparation of trial protocols, particularly with regard to informed consent. Currently, INSERM has distributed flyers describing the CIC's activities and a booklet on its policies in clinical research. A nation-wide information day devoted to clinical

research was organised in January 2003 (“Rendez-Vous Santé”) through the CIC network, an event targeting patients and patients’ associations. Specific sessions for patients’ associations were organised to train their members in critical reading of study protocols (mission associations de malades/INSERM). Future development of this policy includes guidelines for Good Communication Practice, and a definition of best-adapted communication strategies targeting different populations (patients, professionals, news media, stakeholders). The information should be particularly accessible to patients, in close contact with patients’ associations and involving all clinical research professionals. Training sessions in clinical research for news media professionals should also be organised. Finally, there are still misperceptions in France with regard to public advertisements on clinical trials. As a result, investigators and sponsors rarely dare to use this tool, whereas such information on ongoing trials could help stimulate the enrolment of patients.

## 8.2 Patients’ Associations

The French law (Loi de Santé Publique, August 9, 2004<sup>[5]</sup>) implementing the 2001/20/EC Directive had a substantial impact on the role of patients and patients’ associations in clinical research, as follows: (i) a representative of the patients’ associations will be a member of each ethics committee (CPP); (ii) patients enrolled in a study will be kept informed of the global results of the study, according to a format described in the informed-consent sheet, and will have access to their own medical data collected during the study; (iii) patients’ associations may ask the Competent Authority to communicate data on the study protocol stored on the national database (after acceptance by the sponsor, see 9.1). However, patients’ associations ask for even more transparency, including open registries and open communication of results at the end of the study in order to rule out under-reporting and partial reporting, and to keep patients informed of ongoing studies and of advances in treatment opportunities. They also seek for more training and information on clinical research. The AIDS patients’ associations are actively involved in the design of protocols and the writing of information sheets. Cancer and rare disease are other fields with strong patient participation (see 8.1 and 8.3). However, specific programmes developed to train members of patients’ associations to review protocols led to the spread of this activity (more than 100 associations trained in 2004). Finally, acting at the European level is viewed as a positive opportunity, as regulation and drug registration are mainly driven at the EU level. Here again, some medical fields are better organised (such as the European AIDS Treatment Group [EATG] for AIDS, or the European Organisation for Rare

Disorders [EURORDIS] in rare diseases) than others to act at the European level with the aim of stimulating research and facilitating the access to new treatments.

## 8.3 Orphanet as a Communication Tool

Although initiated in France, Orphanet is a Europe-wide organisation covering 20 countries, funded by both DG Research and DG Health. Its activities cover study registers (see 9.4) and communication with the main actors in biomedical research, i.e. patients and patients’ associations, scientists and investigators, and sponsors. Orphanet collects, and provides free access to, information on both experimental and clinical research in rare diseases and orphan drugs (see 9.4). Circulation of information is stimulated through a newsletter (Orphanews) and through a database (OrphanXchange) for experimental programmes, leading to potential clinical/industrial development. Finally, volunteers for clinical trials can register, and an online enrolment service calls these volunteers whenever studies are carried out in the corresponding rare disease.

## 9. Study Registers

### 9.1 French Implementation of the EudraCT Database: Towards Open Access?

The French Competent Authority for medicinal products, medical devices and bioterapy trials (Afssaps) has developed an open database for clinical trials derived from EudraCT content. This is the first open clinical trial register currently managed by a Competent Authority. This information has been available in the French language<sup>[7]</sup> since October 2002. This study register deals with rare diseases, and a serious disease (hepatitis). However, this database currently lacks comprehensiveness as sponsors are initially asked if they are willing to register their study on the database. Currently, about half of the sponsors have not answered, or have responded negatively, but this ratio will probably decrease as the French law (9 August 2004<sup>[5]</sup>) implementing the 2001/20/EC Directive states that refusal to openly register should be justified by appropriate reasons and cannot be systematic. As a result of the new law, this clinical trial register will extend to each authorised clinical trial, and the dissemination of the summary and results is currently being discussed.

Finally, this initiative could possibly spread in Europe, making EudraCT a possible source of an open database, as the Commission currently considers which data derived from EudraCT can be made publicly available (regulation CE/726/2004 Art 57-2).

## 9.2 Towards a National Register for Clinical Research

A brief attempt to set up a French Cochrane database was eventually abandoned because of the lack of financial support. Apart from Afssaps, many institutions have developed their own database for the clinical studies they sponsor, including INSERM, ANRS, or FNCLCC, covering various fields of activity, such as medicines trials and genetic, epidemiological, pathophysiological, diagnostic research and surgery or medical device trials. A common registry based on compatibility and shared standards would increase the attractiveness of French clinical research by targeting patients (fostering enrolment), investigators (benchmarking leading to a better awareness of the state of the art on a given topic), and funding organisations or industry sponsors. A definition of such standards is currently in progress, and will require financial support for completion of an effective national register steered by Afssaps and INSERM.

## 9.3 French Clinical Research and the International Committee of Medical Journal Editors (ICMJE) Initiative

The International Committee of Medical Journal Editors' (ICMJE) statement<sup>[8]</sup> that study registration at inception is a prerequisite for publication received a positive opinion from French public research and regulatory authorities, as French regulations have already played a leading role in promoting transparency for clinical studies through both open study databases and the public availability of results. Some information from EudraCT will be made publicly available in France, unless the sponsor provides convincing arguments for its refusal (see 9.1). Moreover, the French legislation now states that patients enrolled in a study will be kept informed of the global result of the study (see 8.2).

However, its implementation raises practical problems, as no such tool currently exists in France (see 9.2). This will both stimulate the organisation of a national system for study registration, and place this national initiative in a global context. Among others, the language issue needs to be addressed, as a strictly global database in English would prevent patients from having open access to the information on current protocols. Compatibility of a national tool with a European content (EudraCT-derived?) and a global identification system would probably best fit with the French expectations.

## 9.4 Orphanet and Study Registration

Orphanet is a Europe-wide communication tool (see 8.3) covering orphan drugs and rare diseases. Its contribution to clinical study databases is based on the following: (i) a registry of clinical trials on rare diseases, using information collected from investigators and sponsors; and (ii) starting in 2005, a database

on the development of orphan drugs from drug design to market availability, in partnership with the European Medicines Agency (EMA; the Committee for Orphan Medicinal Products [COMP]), the European Federation of Pharmaceutical Industry Associations (EFPIA) and EURORDIS.

## 10. Education and Careers

### 10.1 Careers in Clinical Research

A working group recently released an update on the status and career opportunities in public clinical research, pointing to the need to better define and harmonise the status of staff in clinical research and their careers. This is particularly relevant for participants in clinical research other than senior clinical investigators or pharmacists, whose status is well defined in the hospital system. Although the status of nurses is also well established in hospitals, the function of a study nurse lacks a specific framework (and a working group devoted to study nurses' activities was initiated within the CIC network). In turn, personnel acting as data managers, biostatisticians, quality managers, study monitors or clinical research assistants (ARC, support for sponsors in data monitoring and quality control), clinical research technicians (TRC, support for investigators), and project managers lack a well recognised status. Currently, 700 to 750 personnel in these categories work in hospitals, and there are substantially more if we consider that others are paid by investigators through funds managed by associations. Some are located in clinical departments, some in the offices of the hospital sponsors (DRC), and others in clinical research infrastructures (UEC, CIC). Most of them (75%) are employed under short-term contracts, depending on the specific project, with major discrepancies in their status and salaries, from one hospital (and one project) to another. Heterogeneity in training, and the lack of a uniform graduation system recognised by the hospital administration strengthen such discrepancies. This leads to an unstable employment market, whereas clinical research projects usually last for many years. Although the need for such skills in hospitals remains uncovered, low salaries and poor stability lead clinical research personnel trained by hospitals to seek better job opportunities in the industry.

### 10.2 Training in Clinical Research

Various programmes aim at training investigators and clinical research professionals in France. These courses are usually developed in universities, in close connection with CICs and UECs, and include practical training performed, among others, in CICs and UECs. However, the corresponding degrees are not

always taken into account in the careers of staff members (see 10.1). In spite of the wide diversity of existing programmes, only a few have European connections. In turn, the main national programmes (listed in sections, 10.2.1 to 10.2.4, although some other exist at the local level) are based on cooperation between several universities, thus participating in the harmonisation of training throughout France. These programmes target investigators and pharmacists, staff members acting in methodology, biostatistics, and data management, clinical research assistants, technicians, and study nurses.

#### **10.2.1 Investigators, Medical Doctors, Pharmacists**

Among the training programmes proposed to investigators, DIUs (Diplômes Inter-Universitaire) are based on cooperation between universities. The DIU FIEC (Formation des Investigateurs aux Essais Cliniques des Médicaments) involves seven universities and targets investigators (180/year), combining teaching sessions and a 6-week practical training course. The DIU PEP (PharmacoEPidemiology) involves nine universities and provides MDs or pharmacists with training in pharmacoepidemiology, pharmacovigilance, pharmacoconomics, and risk-to-benefit assessment. Specific training on the scientific content of clinical research protocols is proposed through a 32-hour module in a Public Health Master programme in Paris. Additional programmes are under development, including an online teaching programme in clinical research coordinated by ISPED.

Finally, the European Diploma in Pharmaceutical Medicine (EUDIPHARM) is based on the cooperation of 14 European universities, steered by Lyon, in partnership with regulatory authorities (including the EMEA) and the pharmaceutical industry. Basic and specialised teaching modules are provided in English to students either in Lyon or in Brussels.

#### **10.2.2 Methodology, Biostatistics, Data Management**

Both professional and research training programmes exist in the fields of methodology, biostatistics, and data management. Professional training covers different degrees (from bachelor to master degrees). In particular, the master degree is proposed in some 'engineering schools' (ENSAI, Rennes; ISUP, Paris), and universities, such as Bordeaux 2 (public health), Grenoble (mathematics and computer sciences), Paris 5, 11, 12 and Versailles (public health), and Vannes (mathematics and computer sciences).

Research training in this field is also proposed as a master degree by different universities, such as Bordeaux 2, Lille 2, Lyon 1, Paris 6 and 7, Paris 5, 11, 12 and Versailles. These universities propose advanced training in different specialities such as biostatistics, biomathematics, methods in clinical pharmacol-

ogy, methods in clinical research, methods in clinical epidemiology and modelling in clinical pharmacology and epidemiology.

#### **10.2.3 Clinical Research Assistants and Technicians**

The DIU FARC (Formation des Assistants de Recherche Clinique) was created at the national level in 1988 through the collaboration of seven universities. This training programme, both theoretical and practical, targets students with a bachelor degree but is also open to study nurses. The corresponding qualification – clinical research assistant (ARC) or technician (TRC) – allows students (currently 100/year) to be hired in the pharmaceutical industry or in the academic clinical research (see 10.1).

#### **10.2.4 Study Nurses**

As stated above, the DIU FARC is open to nurses, particularly those working in CICs. However this training is not specifically for study nurses and the degree has little or no influence on their careers. The status of study nurses requires harmonisation at the European level. Currently, the nursing diploma is not considered equivalent to the bachelor degree, preventing nurses getting access to master training in France. Therefore, pilot programmes (Ecole Montsouris, Paris) will be initiated in order to allow study nurses to enter either a 1-year (introduction to clinical research) or a 2-year master level training (clinical research in nursing care). This, however, raises the issue of funding for nurses who are required to interrupt their professional activity during these periods.

## **11. Concluding Remarks**

Some points were discussed while concluding the meeting: (i) The historical development of centres and networks, as well as their multiple partnerships, may account for their diversity. However an effort is now needed to simplify and clarify their respective roles and organisation at the national level. Among other diversity factors, the issue of scientific evaluation and GCP audits has to be addressed; (ii) Ethical principles based on an increased transparency and a better involvement of patients and patients' associations represent a major milestone in the near future of clinical research; (iii) The new regulatory framework for clinical research challenges the role of public sponsors, and questions the capacity of public institutions to maintain or to develop their activity as public sponsors. This could lead to a concentration of public sponsorship capacity within a restricted number of sponsor agencies in a given country. Moreover, the role of public institutions acting as a single sponsor at the European level will require support in specific activities, including data monitoring, adverse-event notification, drug dispensing or regulatory affairs

– and such services facilitating transnational studies represent one of the long-term objectives of ECRIN.

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Correspondence and offprints: *Jacques Demotes-Mainard*, Coordinator, ECRIN Programme, European Clinical Research Infrastructures Network, CIC INSERM-CHU de Bordeaux, CHU Haut-Lévêque, 33604 Pessac, France. E-mail: [demotes@bordeaux.inserm.fr](mailto:demotes@bordeaux.inserm.fr)



**Appendix I. Glossary of acronyms**


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ABID : avec bénéfice individuel direct	AFM : Association Française contre les Myopathies
Afssaps : Agence française de sécurité sanitaire des produits de santé (medicines agency)	AIDS : Acquired ImmunoDeficiency Syndrome
ANRS : Agence Nationale de Recherches sur le SIDA	AP-HP : Assistance Publique – Hôpitaux de Paris
ARC : Attaché de Recherche Clinique	ARH : Agence Régionale de l'Hospitalisation
BECT : Bureau d'Etudes Cliniques et Thérapeutiques ( <i>coordination of clinical research among the FNCLCC</i> )	CCPPRB : Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale ( <i>former ethical review board</i> )
CCTIRS : Comité Consultatif sur le Traitement de l'Information dans la Recherche en Santé	CEA : Commissariat à l'Energie Atomique
CHU : Centre Hospitalier Universitaire	CIC : Centre d'Investigation Clinique
CLCC : Centre de Lutte Contre le Cancer	CNIL : Commission Nationale Informatique et Libertés
CNRS : Centre National de la Recherche Scientifique	COMP : Committee for Orphan Medicinal Products ( <i>EMEA</i> )
COSSEC : Comité d'Orientation Stratégique et de Suivi des Essais Cliniques	CPP : Comité de Protection des Personnes ( <i>new ethical review board</i> )
CRAM : Caisse Régionale d'Assurance Maladie	CTU : Clinical Trials Units
DGS : Direction Générale de la Santé ( <i>Ministry of Health</i> )	DHOS : Direction de l'Hospitalisation et de l'Offre de Soins ( <i>Ministry of Health</i> )
DIU : Diplôme InterUniversitaire	DRASS : Direction Régionale des Affaires Sanitaires et Sociales
DRC : Délégation à la Recherche Clinique	EATG : European AIDS Treatment Group
ECRIN : European Clinical Research Infrastructures Network	EFPIA : European Federation of Pharmaceutical Industry Associations
EMEA : European Medicines Agency	EPST : Etablissement Public à caractère Scientifique et Technique ( <i>public scientific agency</i> )
EU : European Union	EUDIPHARM : European Diploma in Pharmaceutical Medicine
EURORDIS : European Organisation for Rare Disorders	FHF : Fédération Hospitalière de France
FNCLCC : Fédération Nationale des Centres de Lutte Contre le Cancer	GCP : Good Clinical Practice
ICH : International Conference on Harmonisation	ICMJE : International Committee of Medical Journal Editors
INRA : Institut National de la Recherche Agronomique	INSERM : Institut National de la Santé et de la Recherche Médicale
ISPED : Institut de Santé Publique, d'Epidémiologie et de Développement, Université de Bordeaux-2	LEEM : Les Entreprises du Médicament
MD : medical doctor	MeDRA : Medical Dictionary for Regulatory Activities
MIG : Missions d'Intérêt Général	ONIAM : Office National d'Indemnisation des Affections Iatrogènes et des Infections Nosocomiales
PHRC : Programme Hospitalier de Recherche Clinique	PPF : Plan Pluri-Formation
RFUEC : Réseau Français des Unités d'Essais Cliniques	SBID : sans bénéfice individuel direct
SOP : Standard Operating Procedure	SUSAR : suspected unexpected serious adverse reaction
T2A : Tarification à l'Activité	TRC : Technicien de Recherche Clinique
UEC : Unité d'Essais Cliniques	

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