

White Paper
CLINICAL RESEARCH IN FRANCE
AN INTRODUCTION



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1. Introduction

In France, the process for submission and approval by the Ethics Committee and the Competent Authority is well defined. However, the requirements of other stakeholders must also be met before your study can start. And since the publication of the “Sunshine Act” decree in May 2013, the process for contracting with the investigational sites became more complex.

Here, Martine Roggemans shares her knowledge of clinical research in France, describing both the landscape for clinical research and introducing the regulatory processes involved.

2. The Regulatory Landscape in France

All laws and decrees relating to the review and approval of clinical research studies are published on the website of the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) [http://ansm.sante.fr/Activites/Medicaments-et-produits-biologiques/Reglementation-francaise/\(offset\)/3](http://ansm.sante.fr/Activites/Medicaments-et-produits-biologiques/Reglementation-francaise/(offset)/3). The reader will find them clearly presented and classified by topics. The French regulations integrate the transposition of the European Directive on Medicinal Products 2001/20/EC and on Medical Devices 93/42/EEC.

All approval procedures hereunder described are free of charge and either the sponsor or delegated CRO can sign and submit the application forms.

Competent Authority Approval in France

Interventional studies are submitted to the ANSM. Together with the EudraCT number, a document will be completed for the national register of authorized clinical trials in France. All other studies (medical device, biological sampling and observational studies) are registered on line via the ANSM web site and the study will be identified with this registration number on the application forms. Two ANSM application forms will be completed (named “Formulaire 1” and “Formulaire 2”), with additional forms for specific topics as required (biological sampling, use of narcotics, import license, declaration to the public register of clinical trials).

Ethical Approval in France

The type of study to be performed determines whether application is made to an Ethics Committee CPP (Comité de Protection des Personnes). Currently, registry and observational studies should not be submitted to a CPP, but instead to the CCTIRS (Comité Consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé) <http://www.enseignementsup-recherche.gouv.fr/cid20537/cctirs.html>. This will change as



soon as the new law (Loi Jardé) becomes effective after the publication of the decrees of application (expected in 2014). This law extends the role and the responsibilities of the CPPs, such that they will assume responsibility for approval of all types of clinical studies.

Applicants must submit to a single CPP will provides an opinion effective for the all research sites included in the application. The CPP receiving the submission is chosen from any of the 40 CPPs accredited by law. Often, the CPP is located locally to the national coordinator, but this is not mandatory. It is worth noting that the CVs of all Investigators and Sub-Investigators involved from all sites included in the study must be present in the submission to the chosen CPP. This is worth bearing in mind and is it worth prioritizing collection of these CVs at a very early stage, particularly during pre-study/qualification visits!

Data Protection Approval

According to the French law on computerization and liberties (6 January 1978 and updates), two committees are in charge of the protection of data privacy through the survey of the management of confidential data in medical research: the CCTIRS (Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé) and the CNIL (Commission Nationale de l'Informatique et des Libertés).

<http://www.cnil.fr/vos-obligations/declarer-a-la-cnil/declaration/mon-secteur-dactivite/>

<http://www.enseignementsup-recherche.gouv.fr/cid20537/cctirs.html>

An application form will be submitted to the CCTIRS and the CNIL will be notified by a so named "simplified" declaration of biomedical research available on the CNIL website. See the link for the on line declaration:

<http://www.cnil.fr/documentation/fiches-pratiques/fiche/article/une-procedure-simplifiee-de-declaration-pour-les-recherches-biomedicales/>

Site Contract Negotiation

Since the Law Bertand of December 2011 (similar to the Sunshine Act in the USA), the role of the National Council of Physicians (Conseil National de l'Ordre des Médecins, CNOM) has

been reinforced to ensure that reasonable fees are paid to the health professionals and to review the content of the contracts with physicians and sites. Complete transparency is now mandatory on financing between the industry and all health professionals, including hospitals, study coordinators, professional associations and physicians. The physician's fees must be paid via a bi-partite contract with the physician or a tri-partite with the physician and the hospital. Associations are not allowed anymore to receive payments for tasks performed by a physician.

A full dossier together with a request for advice will be submitted to the CNOM two months before any site initiation in France. Therefore, we strongly advise to start the contract negotiation process with each site as soon as possible in the start-up phase of each study. The contracting process with the research sites in France is often very time consuming, because of several contact persons (contract with hospital, contract with the pharmacy, contract with the investigator(s), etc.) and also because the costs and fees are not harmonized. An initiative to improve matters has been launched by CeNGEPS (the National Centre for the Management of Clinical Trials) by providing national templates for contracts with hospitals, and a breakdown table for the calculation of the hospital costs (see the website <http://www.cengeps.fr/en/node/122>).



The CNOM will must also deliver an approval in case of an event organized with physicians (such as an Investigators' Meeting), based on a dossier which must be submitted and approved at least one month before the event. <http://www.conseil-national.medecin.fr/>

Timelines of the approval processes

The ANSM will provide its decision (with one clock stop for questions) within 30 to 60 days (14 days for Phase I trials), or within 90 days for cell, xenogenic, gene therapy or research with genetically modified organisms (GMO).

The CPP (Ethics Committee) will provide its opinion within 35 days (with one clock stop for questions), the CCTIRS (data protection) after one month and the CNIL (data protection) is a notification only. The CNOM will provide its opinion after two months, with frequent clock stops for additional requests (therefore we recommend to start the CNOM process as soon as possible).

3. The Future of Biomedical Research in France

According to the LEEM (French Drug Enterprises Association) in its survey of activity in 2012^{2,3}, it is currently difficult for France to keep its position within the now very competitive international clinical research market. France remains highly active in clinical research into therapies for cancer and orphan diseases, however it is less active than other

comparable European countries in two other main research areas: cardiovascular disease and diabetes.

The annual survey of the clinical research environment in France conducted by LEEM in 2012 involved 30 companies, comprised of both companies with headquarters in France and French affiliate offices of international companies. Respondents were asked to provide data which allowed the authors to assess the attractiveness of France as a location for clinical research. With respect to recruitment into all studies undertaken by the respondents globally, France contributed 6.5% of the 247,000 such subjects (7.6% in 2010). France was responsible for 3.9 subjects recruited per active center in oncology (which was equal to the average across all countries), and 4.2 subjects recruited per active center in orphan diseases (ranked in fourth place globally).

In this competitive context, a multi-disciplinary initiative supported by the government, is working to sustain the excellence of biomedical research in France⁵. Professionals from the Pharma, Medical Device and Biotech industries have created strong relationships for a new industrial deal⁴. The main objectives are to support and to develop clinical research in France. The hospital network is also moving to more dedicated teams, trained to become professional in clinical research and assisted by a finance team, like the “Délégation à la Recherche Clinique et à l’Innovation” (DRCI) in the university hospitals.

France remains an attractive country for clinical research. However, due to the complexity of many start up processes in this country, we always advise a careful selection of the participating sites. Key questions include:

- ✓ Do they have a dedicated research team?
- ✓ Is there a structured finance office?
- ✓ Does the principal investigator prefer a bi-partite or a tri-partite contract?
- ✓ Can the site proactively provide the breakdown table of the hospital costs?

By expertly checking these topics at the earliest stage, timelines for the preparation of the submissions and the negotiation of the contracts can be shortened considerably.

4. Summary

France is still an important location for clinical research, and is productive in many therapy areas. Start up activities in France can be quite complex, and the environment is undergoing some changes at present. For this reason we encourage sponsors to commence start up activities in France at the earliest opportunity. Where sponsors are without experienced local clinical research staff in France we encourage them to seek a partner with demonstrated expertise in this area to support their work.

5. References

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2. France's attractiveness for international clinical trials in 2012: Sixth survey assessed by Leem (French Association of Pharmaceutical Companies), 4/12/2012.
3. LEEM, étude prospective sur les facteurs d'évolution de l'industrie du médicament et leur impact à 10 ans sur l'emploi, undated.
4. Public sector: AVIESAN Alliance Nationale pour les sciences de la Vie et de la Santé, created in 2009.
5. Private sector : ARIIS Alliance pour la Recherche et l'Innovation des Industries de Santé, created in 2010 ; AFCROs Association Française des CROs.
6. 20 ans du programme hospitalier de recherche clinique - Discours de Marisol Touraine le 14 Mars 2013 - <http://www.social-sante.gouv.fr/actualite-presse,42/discours,2333/20-ans-du-programme-hospitalier-de,15656.html>.

6. About the Author

Martine Roggemans is Clinical Research Specialist in Submissions and Contracting at CROMSOURCE in Kraainem, Belgium. She started her career in the pharmaceutical industry in 1991, first as a CRA, then as Project Manager in pharmaceutical companies. She joined the CRO industry in 2006, acting as an expert for regulatory submissions and contracting with the investigational sites in Belgium and other Western European countries. Martine can be contacted at martine.roggemans@cromsource.com

7. About CROMSOURCE

CROMSOURCE is a high quality ISO-certified international provider of outsourced services to the pharmaceutical, biotechnology and medical device industries, specialized in clinical development and staffing solutions.

Operating through offices across all regions of Europe and North America, CROMSOURCE delivers a comprehensive breadth of services. We seamlessly move biopharmaceutical products from first in human conducted in our exceptional early phase unit, through all subsequent phases of pre- and post-approval research internationally. Our Medical Device experts oversee projects through regulatory strategy and submission, to pilot and pivotal clinical investigations in Europe and North America. Our Staffing Solutions Team ensures that high quality professionals are available to support your work whenever you need more resources.



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