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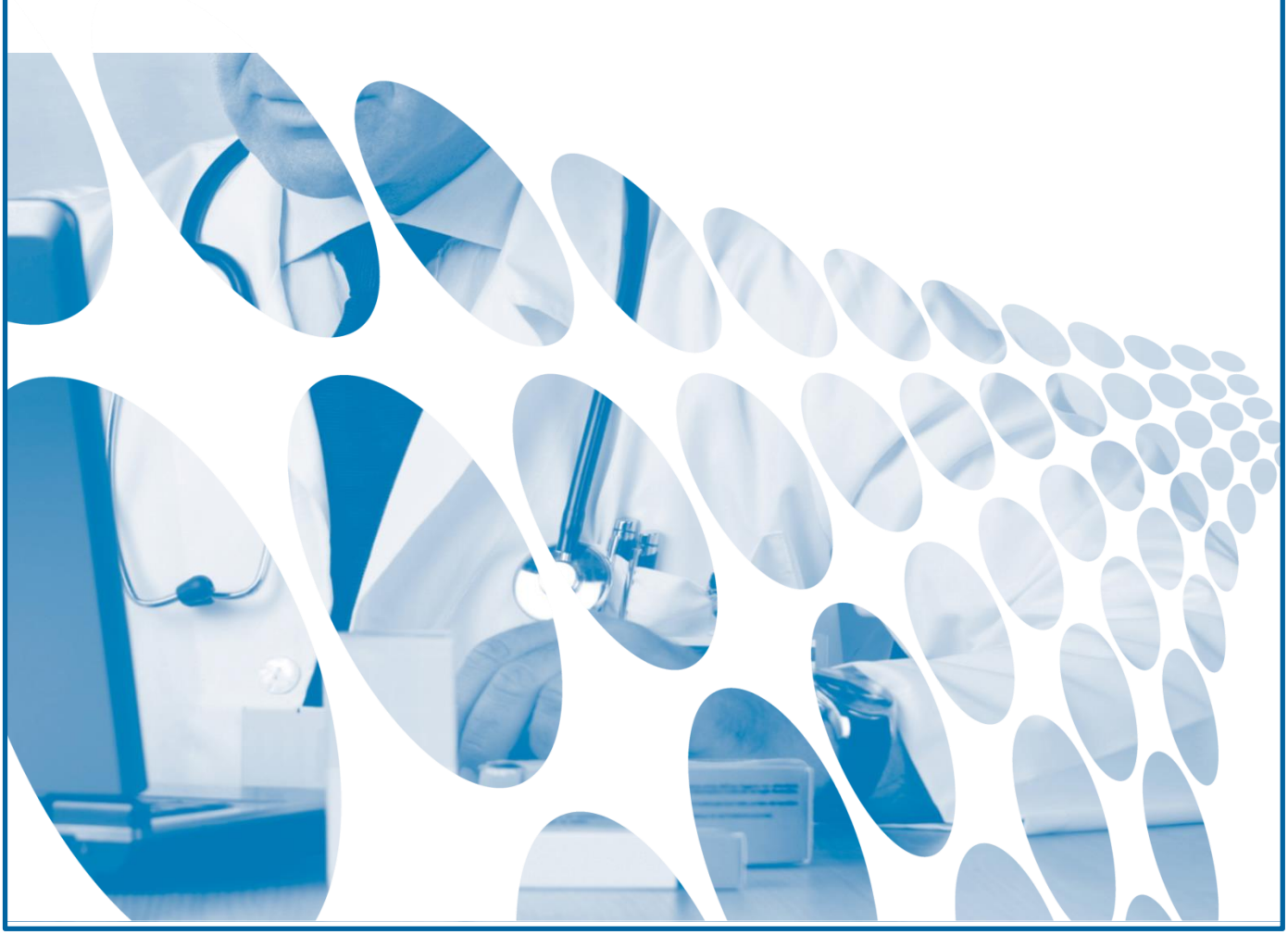
White Paper

CLINICAL RESEARCH IN BELGIUM

AN INTRODUCTION



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1. Introduction

Belgium maintains its excellent reputation in the clinical research world. The nation, which is located right at the heart of Western Europe, boasts many experienced sites which are dedicated to clinical, health professionals at the research sites who possess a high education level, and approval processes for Competent Authorities and Ethics Committees which are performed within short timelines and with reasonable fees.

2. Clinical Research Activity in Belgium

For several decades, Belgium has enjoyed a key position in clinical research. All stakeholders in the clinical research industry are working hard to maintain this situation despite the new challenges of the international clinical research market, and in particular the very competitive areas of Eastern Europe and BRIC countries. The Belgian pharmaceutical sector currently provides 32,000 jobs with approximately 4,600 of those located within the R&D sector [1]. More than 400 industry sponsored clinical trials are performed annually in Belgian centres[2], predominantly within oncology, cardio-vascular, gastroenterology, respiratory, nervous and metabolic diseases. It is notable that per population, Belgium is one of the European countries with the highest participation rate in clinical trials[3].

Since 2010 a formal collaboration, supported by the Federal Agency for Health and Medical Products (FAMHP) has been active. *The Initiative to Promote Clinical Trials in Belgium* is managed by the Belgian Association of Clinical Research Professionals (ACRP.be), the Belgian Association of Pharmaceutical Physicians (BeAPP), the Belgian Association of Phase 1 Units (BAPU) and the Belgian Association of the Pharmaceutical Industry (Pharma.be). Main objectives are to improve the processes for study approvals and to increase the number of valuable patients by the creation of a registry of experts [5, 6]. In this respect the support and interaction of the Belgian health authorities to drive forward actions is crucial to its success.

3. The Regulatory Landscape in Belgium

The Belgian laws and royal decrees related to pharmaceutical and medical device research involving human subjects are published on the website of the Federal Agency FAMHP (http://www.fagg-afmps.be/en/). The Belgian regulations integrate the transposition of the European Directive on Medicinal Products 2001/20/EC and on Medical Devices 93/42/EEC.

Depending on the type of study (interventional or observational, pre-market or post market medical device study), the application will be submitted or not to the **competent authority, FAMHP**. The Agency will provide its approval (with one clock stop for questions) within 28 days (15 days for the phase I trials). This compares favorably with timelines in most other

Western European nations. Furthermore, the FAMHP is most willing to provide support for innovative product research, being very open to meet sponsors and to give advice for the preparation of the dossier prior to submission.

All studies must be submitted to an **accredited Ethics Committee,** normally operating at the hospital of the national coordinator. This accredited EC plays the role of a Leading Ethics Committee (LEC) by coordinating the opinion of the local EC of each participating site. The list of the accredited ECs is also published on the FAMHP website at http://www.fagg-afmps.be/en/. The LEC will provide its single opinion within 28 days (15 days for the phase I trials) with the possibility of one clock stop for questions.

Both applications to Authorities and Ethics can be done in parallel (however, for an investigation with a medical device, the FAMHP will not deliver its approval before having received the written LEC approval).

Fees are chargeable for both FAMHP and ECs and a yearly update on the amounts is published in a royal decree.

4. The Healthcare Landscape in Belgium

Belgium has a great cultural diversity, which has an impact on many aspects of the clinical research performed there. The hospitals in Belgium are sub-divided in two categories: there are currently 141 general hospitals and 68 psychiatric hospitals. Among the general hospitals, 113 are for acute care, with 7 university hospitals and 16 with a link to a university[4].

Smaller hospitals are often merged within a trust, working in close relationships with one of the university hospitals. Besides hospital based research, there is also a very active network of general physicians participating in national and international research studies and programs.

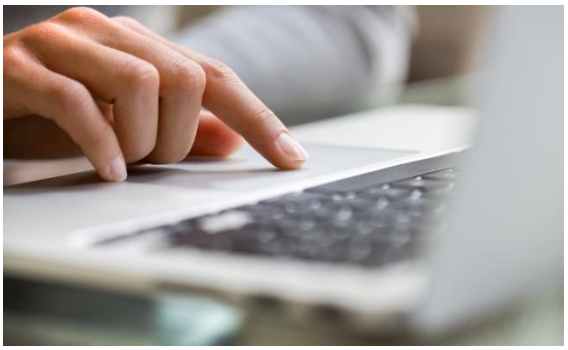
Each hospital must have an Ethics Committee, which means >200 Ethics Committees working in this small country of 11 million people and 36,000 km^2. However, each hospital also has its own statutes, based on the free exam philosophy, on the catholic orientation, or based on management by the Belgian state or by a local city authority. This means that each hospital operates an Ethics Committee which may reflect the individual philosophy of the hospital. To a large degree this explains why in Belgium, positive Ethical Approval for a study requires the opinion of each EC active at each participating centre[7]. The coordination of the submission, review and approval of the individual ECs involved is completed by the above-mentioned Lead Ethics Committee (LEC), which is accredited by law, based on its research activity. Today, 37 Ethics Committees are officially accredited.

Another aspect of life in Belgium which impacts the conduct of clinical research relates to the three official national languages: Flemish, French and German. In practice, all subject

documents (Patient Information Sheet and Informed Consent form (PISIC), questionnaires, diaries, etc.) must be submitted to the EC in both Flemish and French. A German translation will be requested if hospitals located in the Eastern cantons (Eupen, Malmédy, Sankt Vith) are involved in the research. Due to the significant population of workers from other countries in the European Community living in the Brussels metropolitan area, we recommend that approval is also sought for English versions of all study documents provided to research subjects.

In May 2013 an important initiative was launched which with the publication on the FAMHP website of a national template for the PISIC in each of the national languages. We highly recommended sponsors to adopt these templates in order to minimize the likelihood of numerous requests from the ECs which relate to the structure and the wording of this fundamental study document.

As can be seen above, CA and EC approval for clinical research studies in Belgium follows a structured path with well-defined processes and competitive timelines. Prior to study initiation, however, contracts with the research sites must also be negotiated and finalized, a step which does not have mandatory timelines. Although a universally agreed contract template is expected to be published soon, currently the contract negotiation process differs from site. It depends on the structure of the internal hospital approval process, and may or may not involve a legal department. In some hospitals, especially the university hospitals, the process can take some time and we advise sponsors that contract negotiations with sites should be initiated at the earliest opportunity. Indeed, we recommend that sponsors should ensure that they, or their CRO partners, have expertise and experience in achieving contract approval in order to achieve success in the study start up process. Fortunately, a draft contract including a per-subject budget is sufficient for the submission package to the Ethics, with the condition that the budget will be the same for each participating centre. This means that as soon as a site contract is finalized, the site can be opened (assuming EC and CA approvals are already in place). A copy of each signed contract must be provided to the Ethics when available.



5. Why Include Belgium in your Study?

Compared to other European countries, Belgium remains an attractive option for several reasons:

- ✓ Short timelines (28 days) for approval,
- ✓ Reasonable fees for the submissions to CA and EC,

- ✓ Extensive network of expert research sites and workers,
- ✓ Dynamic and supportive national and regional authorities,
- ✓ Federal Agency and EC are very responsive to questions and requests for advice,
- ✓ Due to the small size of the country the distance between the sites is short, facilitating management and travel to the study centers.

6. References

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6. The Initiative, press release 2012 04 17.
7. The current state of clinical ethics and healthcare ethics committees in Belgium, T. Meulenbergs, J Vermylen, P T Schotsmans, www.jmedethics.com .

7. 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

8. About CROMSOURCE

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