Maria João Nunes de Oliveira

Clinical Trials: Portuguese Overview, Perspectives and Competitiveness Challenges.

Dissertation submitted to the Faculty of Pharmacy of Coimbra University, as part of the requirements for the Master Degree in Pharmaceutical Biotechnology. Dissertation guided by Professor Doctor Sérgio Paulo de Magalhães Simões and Co-guided by Professor Doctor Luis Almeida.

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Abbreviations

AIBILI	Association for Innovation and Biomedical Research on Light
BC	Before Christ
BRIC	Brazil, Russia, India and China
CEC	Comissão de Ética Competente (Competent Ethics Committee)
CEIC	Comissão de Ética para a Investigação Clínica (Ethics Committee for Clinical Research)
CIOMS	Council for the International Organization of Medical Sciences
CNPD	Comissão Nacional de Protecção de Dados (National Commission for Data Protection)
CROs	Clinical Research Organizations
CT	Clinical Trials
CTC	Clinical Trial Centre
ECRIN	Europe Clinical Research Infrastructure Network
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FQ	Feasibility Questionnaire
GCP	Good Clinical Practices
GMP	Good Manufacturing Practices
GNP	Gross National Product
ICH	International Conference on Harmonization
INFARMED	Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.
ISF	Investigator Site File
MCT	Multicenter Clinical Trial
MS	Member State of European Union
PNEC	Plataforma Nacional de Ensaios Clínicos (National Platform for Clinical Trials)
PRIM&R/ARENA	Public Responsibility in Medicine and Research/Applied Research Ethics National Association
PtCRIN	Portuguese Clinical Research Infrastructure Network
QMS	Quality Management System
R&D	Research & Development
SMO	Site Management Organization

SOP	Standard Operating Procedures
TMF	Trial Master File
USA	United States of America
WE	Western Europe
WHO	World Health Organization
WMA	World Medical Association
4C	Coimbra Coordinating Centre for Clinical Research

Abstract

Clinical trials (CT) are fundamental to develop new medicines. Clinical trials are the gateway between scientific research and clinical practice. These phases have great importance as they stand for a keystone for economy, providing patients with early access to innovative medicines.

The aim of this dissertation is to study the Portuguese reality concerning clinical trials and to evaluate the number of clinical trials, submitted for approval in Portugal. The author also compares Portugal with other European Union (EU) member states, with United States of America (USA) and with emerging markets. The main objective is to find the reasons for the present situation and try to bring together the necessary alterations to change the negative trend. For this to occur it is important to understand the laws and regulations in this area and be acquainted with the main difficulties that the intervening elements face in a clinical trial (sponsors, investigators, clinical research sites, participants, Clinical Research Organizations, Authorities and Ethics Committee).

Portugal has a strong potential growth in this area. However, in order to improve the Portuguese position in the clinical trial field, scientific and economic support is needed. Therefore, it is urgent to set Portugal at the heart of clinical research along with a competitive position within Europe.

Resumo

Os ensaios clínicos são uma etapa fundamental no desenvolvimento de novos medicamentos. Os ensaios clínicos são a ponte entre a investigação científica e a prática clínica adquirindo uma importância fundamental por serem a primeira oportunidade dos doentes acederem a tratamentos inovadores e por terem impactos económicos muito importantes.

Com esta dissertação pretende-se analisar a situação portuguesa relativamente aos ensaios clínicos focando o número de ensaios realizados em Portugal, comparando Portugal com outros países, realçando as razões e os pontos críticos para a situação encontrada, destacando desafios e oportunidades e compilando algumas iniciativas possíveis e necessárias. Para tal é importante analisar o enquadramento regulamentar da investigação clínica e conhecer as principais dificuldades que sentem os intervenientes nos ensaios clínicos (Promotores, Investigadores, Centros de ensaios, Doentes, Clinical Research Organizations, Autoridades e Comissão de Ética), desde o início ao fim do ensaio.

Portugal tem um grande potencial de crescimento nesta área que não pode ser desperdiçado para que a situação científica e económica evolua. É urgente colocar Portugal no centro da investigação clínica, com uma posição de destaque na Europa.

I. Clinical Trials Introduction

I.I. Role of Clinical Trials in Medicines Development

Clinical research can be grouped in interventional studies (clinical trials) and non-interventional studies (observational studies). This dissertation focuses on clinical trials only. Clinical Trials can be defined as any type of investigation on human-beings in order to discover or verify the clinical, pharmacological and/or pharmacodynamic effects of any medicinal product, its adverse reactions and also study its absorption, distribution, metabolism and excretion [1].

Regulatory entities such as European Medicines Agency (EMA) and the Food and Drug Administration (FDA) in the United States are responsible for establishing procedures and rules for drug testing and to ensure their implementation. Some of these regulations will be referred to below.

Clinical trials can be classified according to their clinical development phase or by their objectives (Figure 1). Initial human pharmacology trials provide an early evaluation of short-term safety and tolerability and can provide pharmacodynamic and pharmacokinetic information needed to choose a suitable dosage range and administration schedule. Usually they are followed by therapeutic exploratory studies in relatively small groups of patients with the target indication. Later confirmatory studies are generally larger and longer and include a more diverse patient population. Dose response information should be obtained at all stages of development. Figure 1 demonstrates the correlation between the two classification systems [2].

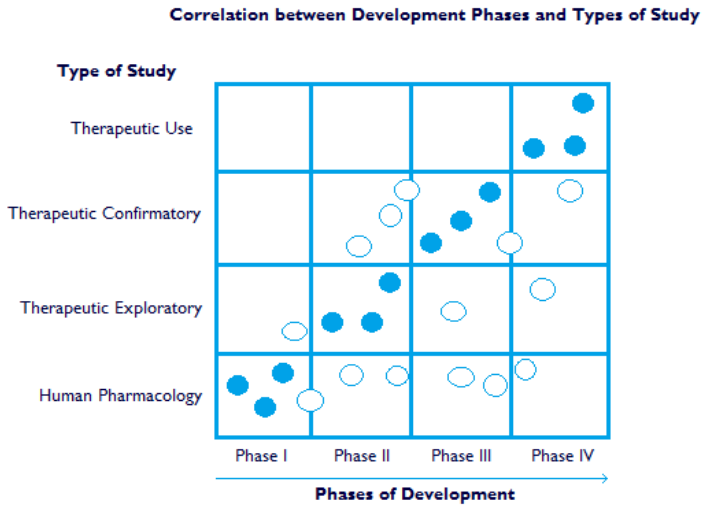

Figure 1: Correlation between the development phases and the types of studies. The shaded circles represent the types of study most usually conducted (by phase) and open circles show certain types of studies that may be conducted, but are less usual. Each circle represents an individual study that includes the objectives, design, conduct, analysis and report. Adapted from source [2].

As can be seen, the types of studies are not exactly synonymous with the phases of development because the typical temporal sequence, described by phase concept, is not appropriate [2].

All new medicines are the result of a long, costly and risky research and development (R&D) process. From the synthesis of a new active substance to marketing approval, an average of 12-13 years will have elapsed. Of every 10,000 substances, only one or two will successfully be marketable medicines. The investment in the conduct of clinical trials represents two-thirds of the cost of developing a new drug (Figure 2) [3].

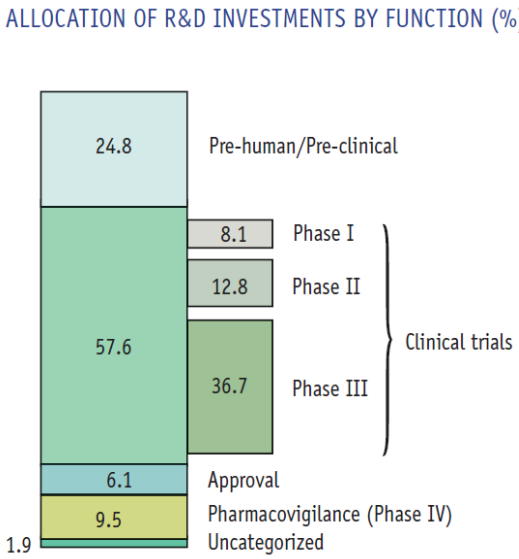

Figure 2: R&D investments. Allocation of R&D investments by function (%). The investment in the realization of CT represents two-thirds of the cost of developing a new drug. Reproduced from source [3].

The high investment in clinical trials, the long development phase and thousands of substances failed and abandoned make the development of a new drug a high risk enterprise, as seen in Figure 3 [4].

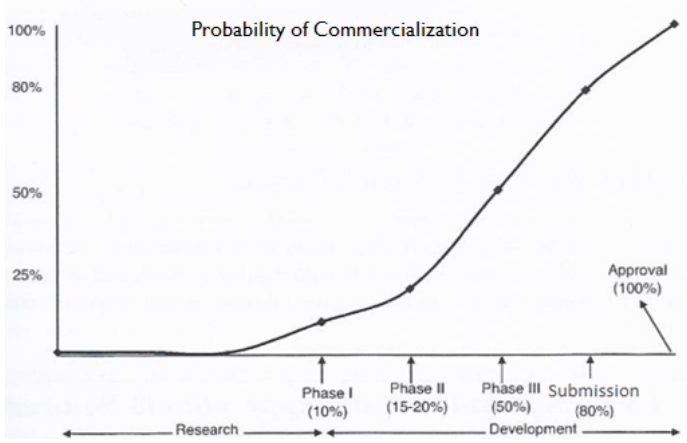

Figure 3: Probability of commercialization. During the research phase of a new drug, the probability of commercialization is residual. In phase I and II the probability increases but only achieves 25%. Even at the time of submission the probability of commercialization is just round 80%. Adapted from source [4].

The final objective of clinical trials is to turn fundamental research into innovative treatments that can be widely available and accessible to people, resulting in increased life expectancy and improved quality of life [3]. For this to happen it is important to articulate the work of all stakeholders involved in clinical trials.

Figure 4: Key group of stakeholders. Stakeholders involved in CT. Reproduced from source [5].

The sponsor is the entity responsible for the implementation and financing of a clinical trial. The sponsor can be an individual, company, institution or organisation [1]. Pharmaceutical companies, the most common sponsors, run in-house clinical trials and/or can outsource (contract an independent organisation to perform tasks) those as well. Contract Research Organizations (CROs) are organizations solely focused and specialized on clinical trials in order to respond to the growing complexity of clinical trials and to improve efficiency in this process [5]. They are sought by sponsors to improve efficiencies, flexibility and to find specific expertise [6].

Healthcare Centres and Hospitals are the sites where clinical trials are conducted. On these sites there are researchers/doctors who are the leaders of the clinical trial [5]. Related to sites, a Site Management Organization (SMO) is a stakeholder that provides clinical trial related services to CROs or directly to sponsors and has the purpose of organizing sites, giving formation to researchers and human resources of the site, implementing harmonized procedures, studying the capacity of sites in terms of patients and clinical areas, and creating a network of sites with forms of action and competences harmonized.

In the end we have the authorities and the patients. The authorities have the responsibility of approving/rejecting the start of a clinical trial, taking into account what is the best for

patients as well as the compliance with laws and ethics. Patients are people that voluntarily agree to take part in the clinical trial [5].

Clinical trials are important for all stakeholders. For the clinical investigator, these trials are the door to new scientific discoveries and they enhance both national and international visibility. For industry, they can represent new medicines in the market and new business opportunities. Finally for participants, clinical trials represent a change of early access to new and better medicines and the improvement of medical support [7]. Clinical trials mean also creation of new jobs and taxes payment. Consequently, they improve the commercial balance reducing public expenditure and inducing value in all activities for the whole chain [8]. The following figure represents key benefits of clinical trials.

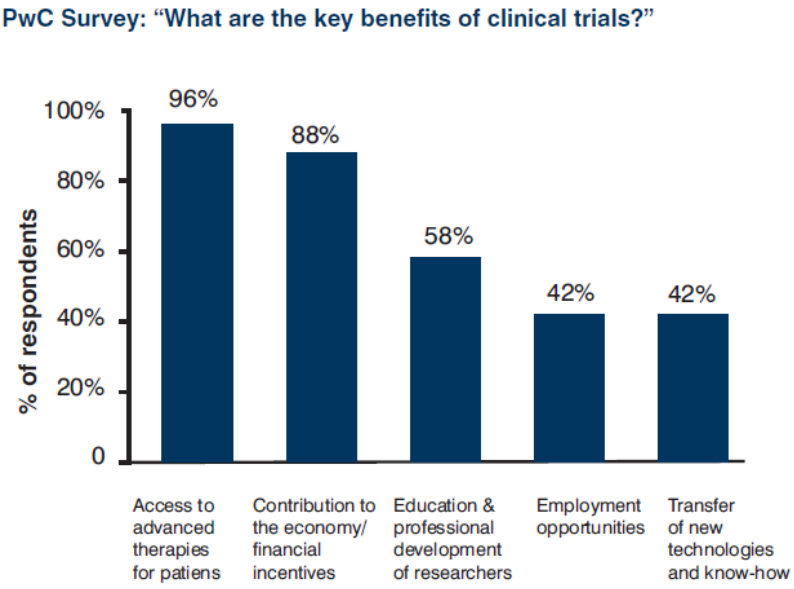

Figure 5: Top 5 advantages of clinical trials. The advantages of the conduct of clinical trials are transversal to all stakeholders. The main advantage is the access to new therapies for patients. Note: Multiple answers available - results do not sum up to 100%. Reproduced from source [5].

Besides all advantages mentioned above, clinical trials can also have a short-term impact on the economy of the city or even the country where they are performed. The economic/financial impact of clinical trials is evident during the interaction of the various stakeholders, as can be seen in Figure 6.

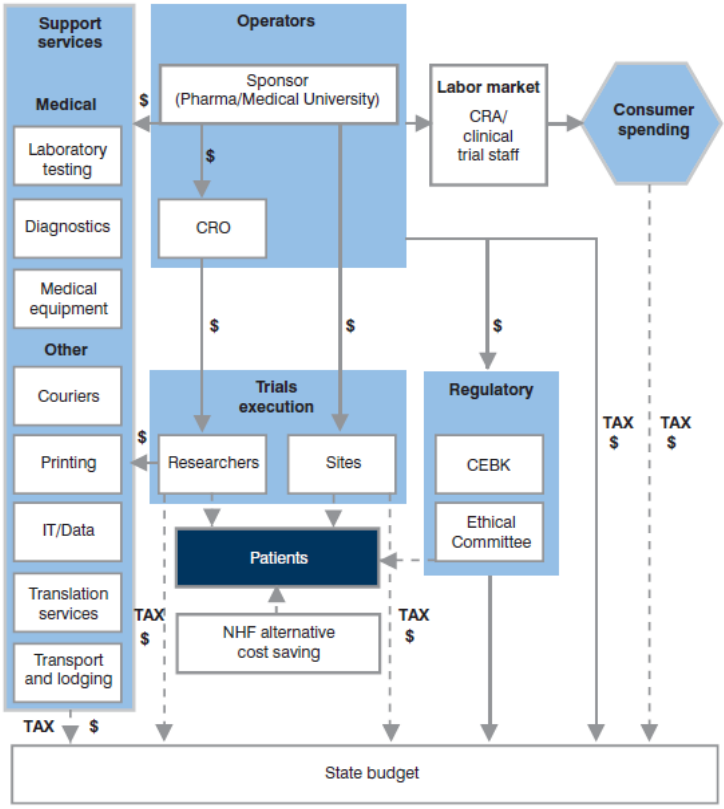

Figure 6: Key impacts on the local economy. The economic/financial impact of clinical trials is evident during the interaction of the various stakeholders. $ is a symbol of a cash flow. Reproduced from Source [5].

There are many factors that influence the choice of where to conduct clinical trials. The location of key partners, access to trial site, internal facilities, future product launches, patient availability, cost efficiency, relevant expertise, regulatory conditions, approval timelines, national infrastructure and market potential are some of the factors that pharmaceutical industry have to take into account when they have to choose a country [9].

Figure 7: Global key drivers for clinical trial location choice. There are many factors that influence the choice of where to conduct clinical trials. Approval timelines, access to patient populations, relevant expertise and cost are the most important factors that sponsors have to take into account when they have to choose a country, according to PwC analysis. Reproduced from source [6].

It is also important to evaluate the interest and ability of the sites to perform a particular clinical trial. For this to occur there is the Feasibility Questionnaire (FQ), which is a small questionnaire that sponsors send to the putative study sites. In this questionnaire the site is required to give information about the physicians with interest in the study, the number of patients that can be recruited for the study and other important information.

One of the most important steps of this process is the recruitment of patients. The consequences of a poor recruitment are transversal to all stakeholders. For sponsors it may cause potentially twisted statistical results, loss of position and/or revenue for product and decline of confidence in investigators. For sites it may bring potential lost revenue for missing targets, risk to future trial participation with sponsor and loss in patient confidence [10].

There are many factors that influence the recruitment and many reasons to participate in a clinical trial. A 2004 European survey found that 68% of the people interviewed would consider joining a clinical trial and two-thirds were motivated "to advance medical science". The other reasons were: "help others with condition" (57%), "obtain better treatment for my condition" (48%) and "obtain faster access to treatment for my condition" (34%). The main reasons for the decline in participation were believed to be: medical treatment would be less effective than standard care, they might get a placebo and they would be treated like a "guinea pig". Travel distance and out-of-pocket expenses were also referred [10].

The aim of this dissertation is to study the Portuguese reality concerning clinical trials and evaluate the number and type of clinical trials submitted for approval in Portugal together with their evolution. The author intends also to compare Portugal with other EU member states (MS), with USA and with emerging markets. The main objective is to find the reasons for the present declining situation and try to bring together the necessary alterations to change the negative trend. For this to occur it is important to understand the laws and regulations in this area and be acquainted with the main difficulties that the intervening elements face when implementing and conducting a clinical trial.

I.II. Historical Perspective

The first reference to health experiments dates back to 605 BC. Old Testament explains how Daniel did an experiment when he refused the diet ordered by King Nebuchadnezzar [11]. However, we can tell that James Lind conducted the first CT in May 1747. After two months at sea, when the ship was afflicted with scurvy, he controlled a group of 12 sailors with scurvy and divided them into six pairs, giving each group different additions to their same basic diet. With this experimentation Lind established the treatment for scurvy [12]. This clinical trial is a relevant milestone for clinical research and the reason why, today, the International Day of Clinical Trial is celebrated in May. After that, clinical trials have been suffering a substantial evolution.

The concept of placebo was introduced in clinical trials as early as in 1799, when John Haygarth conducted a clinical trial with a group of control he named placebo-controlled. However, it was only in 1832 that placebo took on its current meaning of a treatment that has no medical value except psychologically [13]. In 1944 Multicenter Clinical Trial (MCT) was introduced. This is a clinical trial carried out according to a single protocol at more than one medical centre or clinic. MCT is conducted by more than one investigator at several sites. The advantages of these trials are that they include a larger number of participants, different geographic locations and the ability to compare results between centres [1, 14].

It is also important to understand the facts that are in the origin of the ethical concerns and evolution. As early as in 1803 we have references to "Code of Ethics", which can be considered the beginning of ethical concerns. In this year Thomas Percival advised physicians to consult colleagues before trying new medicines and treatments. In 1847, the American Medical Association adopted a code of ethics and in 1902 the book "Medical Ethics" by Albert Moll was edited. After that, the concerns about ethics have improved but only in 1945 were these concerns materialized in a strict regulation resulting in the Nuremberg Code and Helsinki Declaration. These regulations also resulted from the horror at the abuses perpetrated during the World War II and the Nazi human experimentations [13].

Nuremberg Code was created in the wake of the trial of Nazi doctors and it was the first internationally-recognized code of ethics for human research. It establishes ten basic principles for Human protection, centred not on the physician but on the research subject. These principles included an absolute requirement of voluntary informed consent, minimizing risks to subjects, results that are valuable to society and a new right of the subject to withdraw from participation in an experiment. The key contribution of Nuremberg was to

the combination of Hippocratic ethics with the protection of human-rights. Nuremberg Code has influenced global human-rights law and medical ethics [15].

The references to informed consent in medical treatment are much older than clinical research, dating back to 1767 when English court rules considered that informed consent should be prior to medical treatment. Medical treatment influenced the clinical research and the adoption, by the American Medical Association, in 1946, of a code of ethics for research on human-beings that required informed consent. These requirements were intensified in 1962 after the Thalidomide disaster, when it was required to pharmaceutical companies to prove drug efficacy, firms to submit adverse reaction reports to the FDA, drug advertising to include complete information about risks and benefits, and informed consent from clinical study subjects [13].

In 1964 the World Medical Association (WMA) developed the Declaration of Helsinki, which also required informed consent. In contrast to the legal form of the Nuremburg Code, it takes the form of ethical guidelines [16]. The difference is that the Nuremberg Code focuses on the human-rights of research subjects while the Declaration of Helsinki focuses on the obligations of physician-investigators to research subjects. For example, it refers that medical research is subject to ethical standards that promote respect for all human-beings and protect their health and rights especially for research populations that are vulnerable and need special protection like those who cannot give or refuse consent for themselves [15]. However, only in 1967 did the FDA issue a policy clarifying that informed consent must be in writing. By this time, the discussion about this theme was very intense. The book "Human Experimentation: Ethics in the Consent Situation" (discussing issues of informed consent or lack thereof) by John Fletcher, was written and the Public Responsibility in Medicine and Research/Applied Research Ethics National Association (PRIM&R/ARENA) was founded. Also in 1982 the Council for the International Organization of Medical Sciences (CIOMS) published the "International Ethics Guidelines for Biomedical Research Involving Human Subjects", including cross-cultural guidance for conducting research in developing countries, which were updated in 1993. In 2000, the World Health Organization (WHO) issued the "Operational Guidelines for Ethics Committees that Review Biomedical Research" [13]. In 2002, CIOMS prepared, in collaboration with the WHO, a new version of the "International Ethics Guidelines for Biomedical Research Involving Human Subjects" that overtook the guidelines of 1993 and whose core consists of 21 guidelines [17].

Modern ethics for research in humans are based on 3 pillars: Nuremberg Code, Helsinki Declaration and International Ethics Guidelines for Biomedical Research Involving Human Subjects of CIOMS and WHO. In order to standardize the questions related to clinical trials

and the requirements to approve a new medicine, it was created, in 1990, the International Conference on Harmonization (ICH), which is unique in bringing together the regulatory authority of USA, EU and Japan. Since its origin, the ICH has evolved to respond the increasingly global aspect of drug development and the benefits of international harmonization that ensure that safe, effective and high quality medicines are developed and registered in the most resourceful-efficient manner. Six years later, the ICH published "Good Clinical Practices: Consolidated Guideline" that is considered the Bible for conducting clinical trials [18].

In 2001, the Directive 2001/20/EC was put into practice and was introduced in the legislation of all Member States until 2004. This directive will deserve further analysis ahead in this dissertation [1].

II. Clinical Trials Regulatory Framework

As a result of some milestones aforementioned, clinical trials have, today, a strict regulation.
The directive elaborated by the European Parliament in order to approximate laws, regulations and administrative provisions of all MS, related to the implementation of good clinical practice in the conduct of clinical trials on medical products for human use, is Directive 2001/20/EC [1]. This directive brings specifics rules on CT at the EU level. All CT are concerned except "non-interventional" studies [19].
In Portugal the Law nº 46/2004, of 19 August, establishes the legal regime applicable to the conduct of clinical trials with medicines for human use and it transposed into the national legal order the Directive 2001/20/EC [20]. This legislation repealed the Decree-Law nº 97/94, of 9 April, but continues to reiterate the emerging internationals principles with more relevance for biomedical investigation in human-beings, with an emphasis on the Nuremberg Code, Declaration of Helsinki and International Ethics Guidelines for Biomedical Research Involving Human Subjects (of CIOMS and WHO (2002)) [21].
These principles are [15-17]:

- Protect the life, health, privacy and dignity of the human-beings;
- The subjects must be volunteers and have to be informed in one's language or another form of communication that the individual can understand;
- The voluntary consent of human subject is absolutely essential and must not be obtained by pressure, intimidation or payment;
- The interests of the participants have always to prevail over those of science and society;
- The physician shall act only in the patient's interest and has to be qualified persons able to ensure that potential benefits and risks are reasonably balanced and risks are minimized;
- The investigator must establish secure safeguards of the confidentiality of subject's research data;
- The participants have the right to treatment and compensation in case of injury.

Compared the Law nº 46/2004 with previous regime, this new law brought some new aspects.
To INFARMED (Autoridade Nacional do Medicamento e Produtos de Saúde I.P.) it was attributed, through its administration, the power to authorize the conduct of a clinical trial, within a period of 60 days. During this period, INFARMED has to analyse the required documentation sent by the sponsor and conclude that benefits to participants outweigh the

risks. If it is a MCT carried out in more than one country, it is necessary to have identification and approval of all competent authorities. The period of 60 days could be suspended due to requests for additional information or documentation and even extended for special cases when the investigational medicinal product is of biological origin, gene therapy, somatic cell therapy medicinal products, genetically modified organisms and xenogeic cell therapy medicinal products. For the first four, the evaluation period can be extended for more 30 or even 90 days. For the last one there is no deadline. On the other hand, the authorization can be granted tacitly if INFARMED does not provide the sponsor any negative opinion [21].

Asking the permission is an attribution of the sponsor and it has to present its complete identification, the identification and qualification of all the researchers and members of the clinical trials' team, information about the site of realization of clinical trial, protocol, investigator's brochure and the dispositions about indemnities or compensations for possible test damage, insurances to cover the liability of both the investigators and the sponsor and other relevant elements of the financial contract between the sponsor and the trial site [21].

With this legislation INFARMED came to hold the competence to allow clinical trials, instead of to being only informed [21]. INFARMED is also the authority responsible for the inspections of GCP (Good Clinical Practices) and GMP (Good Manufacturing Practices). INFARMED inspectors are empowered to inspect all sites and resources involved in a clinical trial and the sponsor should ensure that they are always ready to be inspected. Failure to comply the terms of law could lead to criminal prosecution of the violator [19]. INFARMED is also the entity that can introduce the national data in EudraCT European database and the responsible for the creation of a data base on clinical trials conducted in national research centres [21].

The new law reiterates the general conditions for the participation and protection of subjects required in previous legislation. Without complying with the following requirements the clinical trial performance is not possible [1, 21]:

- The researcher must clearly inform the participants about the objectives, risks and inconveniences of that type of research, about the conditions of the accomplishment of that clinical trial and must also give the participants right to quit the study at any time, using appropriate language adapted to the capacity of the subject;
- The written declaration of informed consent;
- The assure the integrity and the right to privacy and data protection;
- The assure the right to medical treatment and care by a qualified doctor;
- A contact point where subject may obtain further information;

- An insurance or indemnity to cover the liability of the investigator and sponsor, independent of guilty.

Despite the fact that the previous law also obliges the existence of insurance to compensate the subject, the present law specifies the scope of insurance and clarifies some doubts when it expresses that all health damage of participant during the clinical trial and one year after its conclusion are attributable to clinical trial. However, this insurance doesn't absolve the sponsor, the investigator and all team members of their civil and legal responsibility [21].

For ethical reasons, this legislation has special regulations to protect participants with less autonomy because of immaturity or mental perturbation. To include persons incapable of giving informed legal consent it is necessary [19, 21]:

- The clinical trial has to bring some direct benefit for the participants and this have to be thoroughly evaluated by Ethics Committee for Clinical Research;
- The clinical trial has to be directly related to a clinical condition of the participant and is essential to validate data obtained in clinical trials on persons able to give informed consent;
- Requirements should be taken to minimize pain, fear, risk and distress;
- The informed consent of a legal representative that should reflect the desire of the participant according to his/her capacity of understanding;
- No financial benefits are allowed.

In contrast to the previous law, the Law nº 46/2004 only refers to the prohibition of financial benefits to participants incapable of giving informed legal consent. Relative to capable participants this information is omitted [21].

There are other issues that this law doesn't specify, such as the use of placebo and the participation of healthy people in clinical trials [21].

Despite the fact that the Helsinki Declaration accepts the use of placebo only if no proven prophylactic, diagnostic or therapeutic method exists, in this law there is only one reference to placebo that is the definition of the concept [16].

About the participation of healthy people, this legislation doesn't make any reference to the status of healthy people who want to participate in clinical trials. The previous legislation had a restriction and said that healthy people could only participate if there were no risks to physical and psychic integrity of the participant. This legislation only refers that the potential benefits to participants have to overcome the risks and inconvenience [21].

Another change brought by the present legislation (and Directive 2001/20/EC) was the creation of an Ethics Committee for Clinical Research (CEIC) that has a crucial role in the approval of clinical trials. It is constituted by health professionals and other people that have

technical competencies to evaluate the clinical trial and the conditions for its accomplishment. CEIC has the responsibility of receiving and validating the request for the CEIC opinion presented by sponsor and take a decision about the clinical trial or substantial changes. CEIC can delegate the issuance of the opinion to another ethics committee designated Ethics Committee Competent (CEC). Only one opinion is required by law (opinion by CEIC or opinion by any CEC designated by CEIC by explicit delegation). Therefore, the authorization for conducting the clinical trial is independent from the existence of ethics committees in the entity seeking clinical trial [21]. CEIC or its delegate has 60 days to evaluate and issue an opinion about clinical trials, with an extension of 30 days if there is a request for further information [19].

Concerning the protection of individuals with regard to the processing of personal data and on the free movement of such data, the European Parliament has published the Directive 95/46/EC [22]. The Portuguese legislation that transposes this directive into the national legal order is Law nº 67/98, of 26 October, that establishes particular rules. This law states that the treatment and registration of personal data must respect the privacy and fundamental rights, freedoms and guarantees of the individual. The treatment of health data is forbidden except by authorization of National Commission for Data Protection (CNPD) and with express voluntary consent of the human subject. CNPD has also to authorize the interconnection of personal data. Therefore, the sponsor has to notify CNPD before the beginning of the clinical trial to obtain the authorization for the treatment, registration and interconnection of the data resulting from clinical trial [23].

About investigational medicinal products, those haven't been given any special treatment until this legislation but have now a chapter where all demands and obligations are defined. The manufacturing and import of those medicines have to be authorized by INFARMED and have to be according to the GMP. The authorization holder has to possess a qualified pharmacist responsible person for the medicine. Every control and registration related to medicine must be available. In this law, there is also a description of some rules to proceed to the labelling of the investigational medicinal product [20]. Finally it is important to detach the free availability of the experimental medicine to participant after the end of clinical trial since it is essential to continue treatment and there are not therapeutic alternatives [21].

Clinical trials have to respect every rules, directive and laws summarized above and they have to be made by investigators who have qualifications and GCP training or experience obtained from work with clinical trials and recognised by INFARMED and CEIC. In the procedure to notification a clinical trial, the sponsor must obtain a EudraCT number, according to Detailed Guidance on the European clinical trials database [24]. The competent

authorities and the ethics committee notified by coordinator, sponsor or investigator will be alerted about the study. This notification can be done in parallel or sequentially [19]. The sponsor may not start a clinical trial until the CEIC has issued a favourable opinion and inasmuch as the competent authority concerned has not informed the sponsor of any grounds for non-acceptance [24].

Whenever necessary, protocol amendments that meet the criteria for substantial amendments can be done and must be reported to the relevant competent authorities and ethics committees. Directive 2001/20/EC refers only amendments to the approved protocol and considers substantial amendments when they have a significant impact on the safety or physical or mental integrity of the clinical trial participants and/or the scientific value of the trial. It is up to the sponsor to assess whether an amendment is to be regarded as substantial. The Directive 2001/20/EC doesn't establish a deadline for authorities' response to the amendments. However they are invited to respond also within 35 days [24].

For the end of the trial it is necessary to notify the competent authorities via EudraCT database within 90 days of trial completion or 15 days of premature termination [19].

In Portugal, the INFARMED has a National Platform for Clinical Trials (PNEC) where, in the near future, the application for authorization of clinical trials, respective amendments and the information of the end of the trial can be submitted electronically [25].

Clinical trials may only be conducted in clinical investigative sites with adequate facilities and human resources. The responsibilities are exactly the same for clinical trials sponsored by pharmaceutical industry and those whose sponsors are the investigators who perform the clinical trials [19].

The approval process of clinical trials in Portugal can be summarized in the flowchart presented in Figure 8. After sponsor analysing the clinical trial feasibility, it is necessary to submit the clinical trial to the approval by INFARMED, CEIC and CNPD.

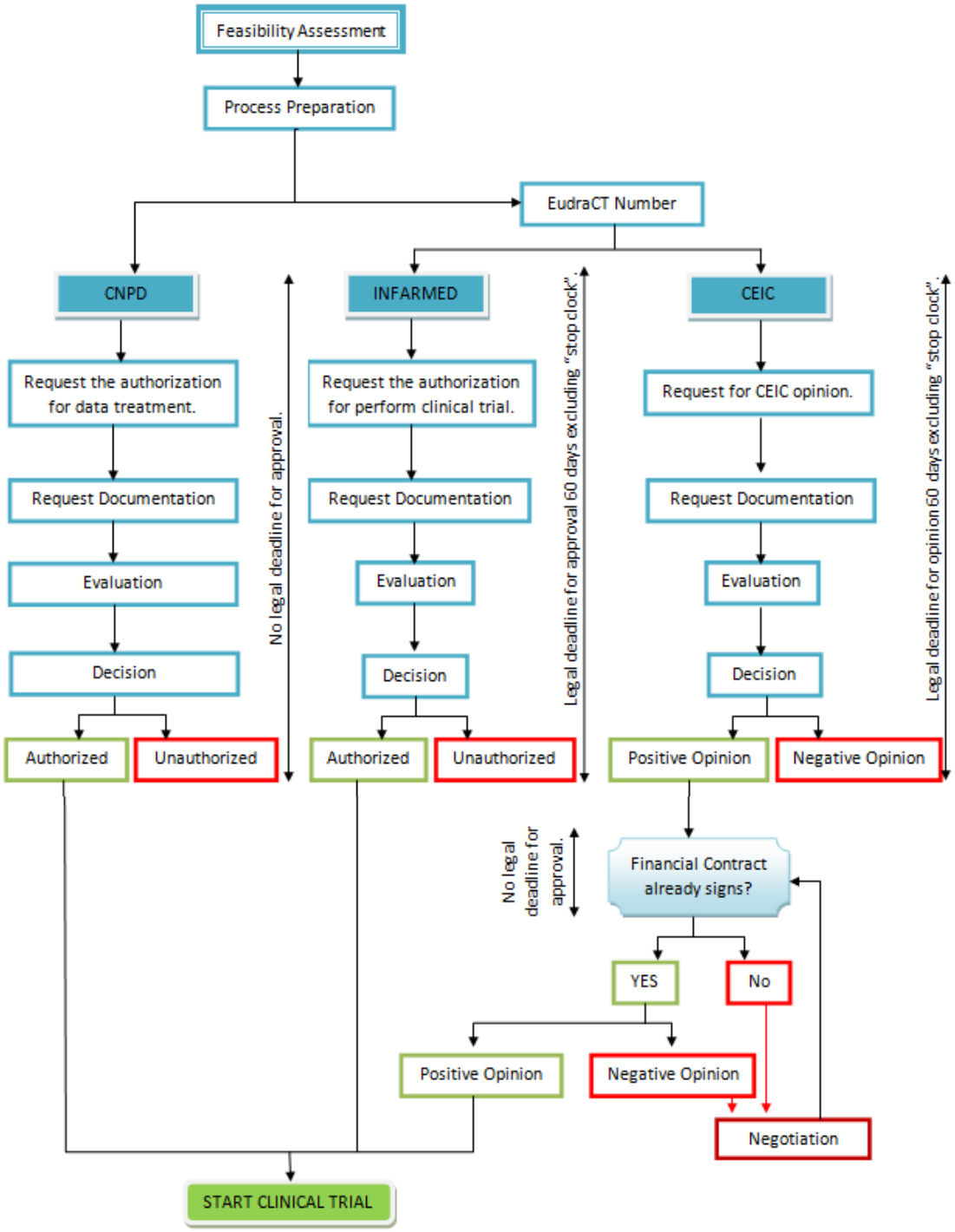

Figure 8: Approval process for clinical trials in Portugal. Representative flowchart of the approval process of clinical trials in Portugal. Adapted from source [8].

III. Clinical Trial Trends

The aim of this chapter is to compile the most important data of clinical research and clinical trials in Portugal. To better understand these data the author starts to frame Europe in the World. In sub-chapter III.I will be presented comparative data of Europe and the rest of the World, in sub-chapter III.II comparative data from Portugal and other similar countries and in sub-chapter III.III the data are related to the evolution of clinical research and clinical trials in Portugal, an overview.

III.I. Europe vs Other Regions

In Europe, the pharmaceutical industry has a significant role in R&D investment. However, the sector faces real challenges because it has been severely hit by the impact of fiscal austerity measures introduced by governments across much of Europe that resulted in pharmaceutical companies R&D spending decline [5]. Figure 9 shows the pharmaceutical R&D investment in Europe comparing with USA and Japan.

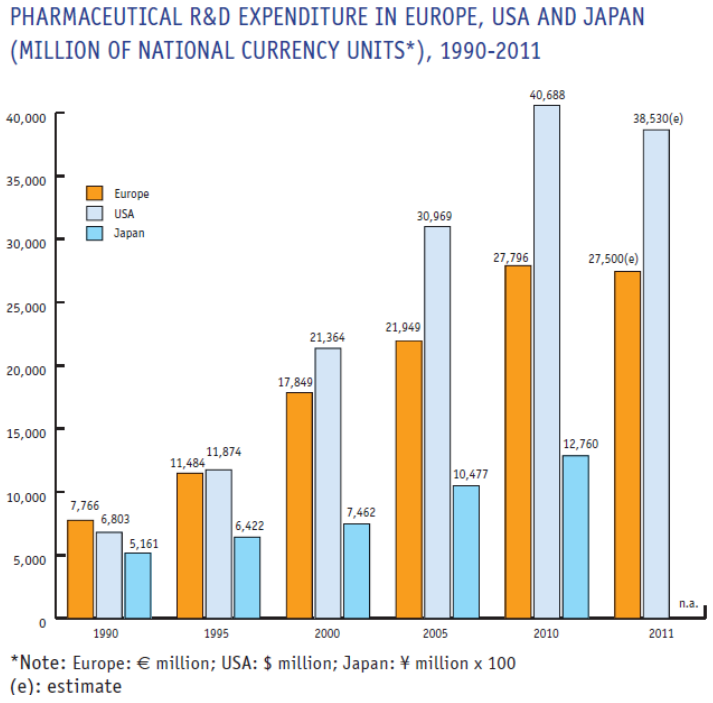

Figure 9: Pharmaceutical R&D investment in Europe, USA and Japan (1990-2011). Representative graphic of pharmaceutical R&D investment in Europe, USA, Japan and other countries. The same trend of the previous graphic. Reproduced from source [3].

One of the major reasons for the investment decrease in Europe is the price control of medicines that are not ruled by free competition laws, but fixed by the governments on a

national basis [6]. However, stricter regulatory approval processes and efforts to contain healthcare expenditures have had a tendency to restrict the growth of markets in Europe. This has resulted in a lucrative parallel trade between countries with significant price differences.

These countries are known by emerging markets [26]. Emerging economies such as Brazil, Russia, India and China (BRIC) have lived a rapid growth in the pharmaceutical market and research environment. In 2011 the Brazilian and Chinese markets grew 20.0% and 21.9% respectively, compared with an average market growth of 2.6% for the five major European markets and 3.6% for the USA market [3]. Europe has been losing competitiveness compared to others regions of the World and it is anticipated that markets in the emerging countries will continue to grow another 14-17% by 2014, compared with 3-6% for developed markets [6].

The investment in R&D has influence in the knowledge obtained and can influence the number of new medical entities. In the graphic below can be analysing the evolution of new medical entities in Europe, USA and Japan.

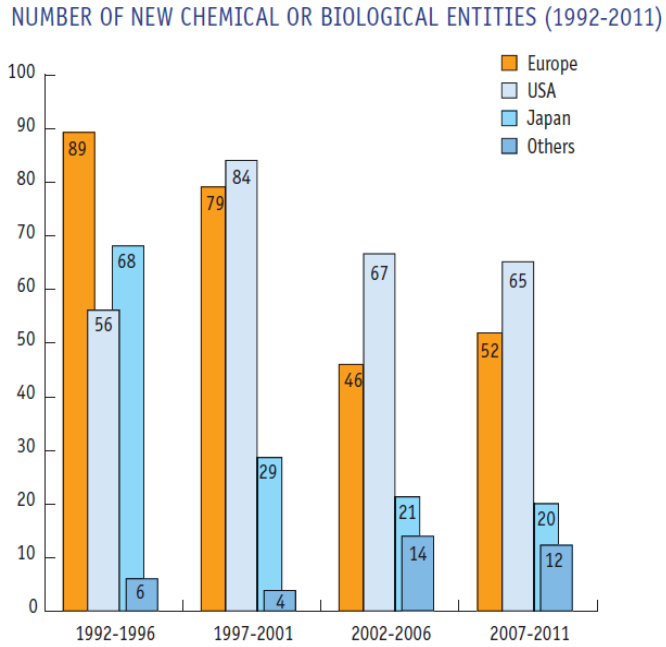

Figure 10: New medical entities (1992-2011). Representative graphic of new medical entities in Europe, USA, Japan and others. Reproduced from source [3].

Figure 10 highlights how the number of new discoveries has been decreasing in Europe. This reduction occurred even in years where the R&D investment in Europe increased. The R&D investment hasn't been translated into new medicines. This is a problem called Translational Gap and it occurs when a lot of R&D investment results in a lot of scientific information that is not translated in applied knowledge and new products [27].

Faced with an increasingly competitive market and an urgency to reduce costs and difficulties of medical product development, the actual development model has to be changed to a more flexible process, based on data [28]. This new model is supported by main regulatory authorities, including FDA, and it has the aims to ensure that, without prejudice of safety, the new drugs can be experienced in human-beings the earliest possible [29]. As can be seen on Figure 11, the new drug development process is expected to be shorter. More emphasis will be given on laboratory research (molecules) and on the robustness of the mechanism and safety of the molecules so that the drug development can be secure and launch "in-life testing", that is a series of small, highly targeted clinical studies. The clinical trials will be more focused on a particular group of patients and the company will be allowed to market the drug on a restricted basis (to a narrow group of patients), upon the regulatory agency's conditional approval [5].

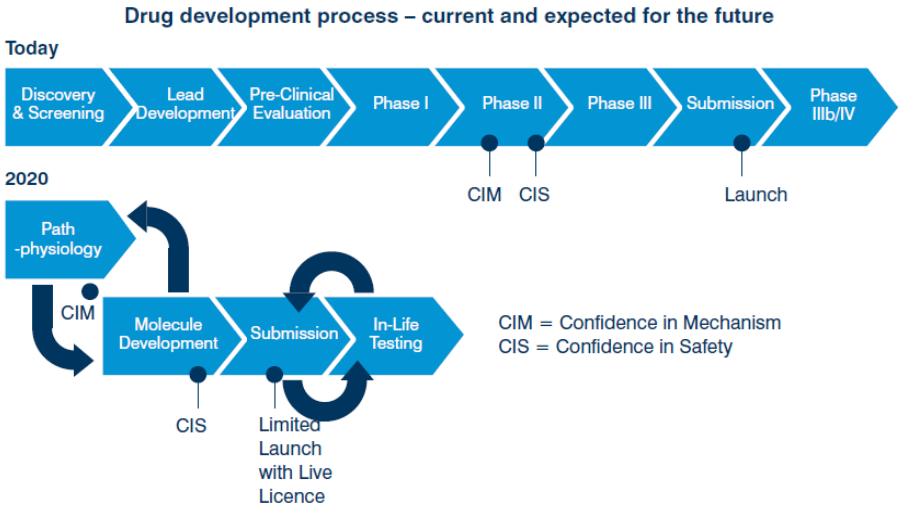

Figure 11: Drug development process comparison. Comparison between current drug development process and the expectation for the future. The new development model is a more flexible process and based on data. Reproduced from source [5].

This new model has to reflect the new paradigm of actuation in the market that is highly affected by: level of market uncertainty, financing difficulties, new markets, high level of current market consolidation that leads to reduced growth opportunities, great competition from generics, aging population and pressure to reduce costs in health systems [8].

Talking specifically about the conduct of clinical trials, the effort of developing new drugs can be tracked, based on worldwide pharmaceuticals pipelines. Analysing the state of these projects, the drugs in development can be known. The trend was year-on-year increases, since 1995. However, in 2011, the total of 9713 drugs in development represented a small decline (0.2%) from the 2010 number of 9737. This decline is insignificant but it would

appear to confirm a trend of a plateauing off the longer-term trend of year-on-year increases [4]. This results from the Translational Gap but is also consequence of a change in the good enough concept. “Ten years ago, if you had a drug that was a little bit better or even as good as something already on the market, you could get it approved. Those days are gone.” Jonathan Knowles (Chairman of the Innovative Medicines Initiative, Head of Research at Roche) [4]. This fact and also the financial restrictions had as consequence the review of all ongoing pipelines by the worldwide companies and the rejection of the unpromising projects that can be also contributed to the plateau phase.

When examined the drugs in active development on a phase-by-phase basis, there are encouraging signs. Figure 12 represents the evolution of the number of drugs in active development since 2007 until 2011. There are now more R&D projects than ever before in clinical trials and all phases saw solid growth. The most robust growth was in phase III. The number of drugs in phase III, in 2011, has shown the biggest year-on-year jump so far recorded, with more 83 than 2010 (13%). This is a positive signal that appears to change recent trend of increases in the numbers of phase 1 and II drugs that failed to transition to phase III [4].

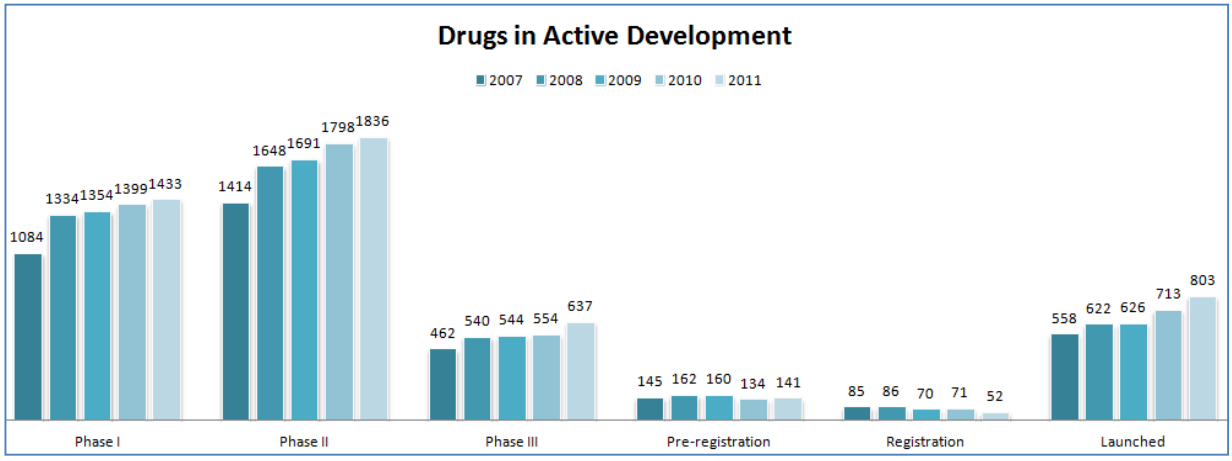

Figure 12: Drugs in active development phase-by-phase (2007-2011). There are now more R&D projects than ever before in clinical trials and all phases saw solid growth. The number of drugs in phase III, in 2011, has shown the biggest year-on-year jump so far recorded with more 83 than 2010 (13%). Adapted from source [4].

The investment in clinical trials represents two-thirds of the cost of developing a new drug. In 2009, it corresponded to reinvestment of an average of 18% of European pharmaceutical companies’ sales into R&D. The percentage share of total R&D budget allocated to clinical trials has increased considerably over the last few years due to the complexity of clinical trials [6].

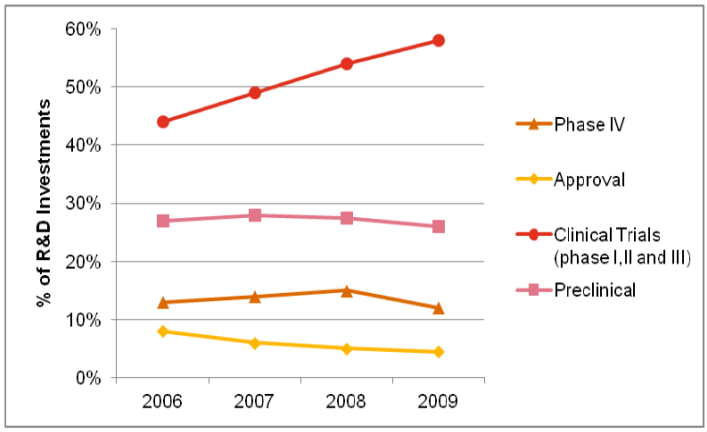

Figure 13: R&D investments allocated to clinical trials in Europe (2006-2009). The percentage share of total R&D budget allocated to clinical trials has increased considerably over the last few years due to the complexity of clinical trials. Reproduced from source [6].

Rising costs and increasing budget pressures have started to affect clinical trials forcing companies to rethink how to perform these activities. The choice of the country that best suits the clinical trial is an increasing concern of the pharmaceutical companies. Depending on the location, cost saving can range from 30 to 65% in emerging markets compared with sites in the United States of America (USA) or Western Europe (WE). Also in these countries the time to complete clinical trials phases is shorter, which provides earlier relief to patients, a faster return on investment, a potential edge over competitors and a longer patent protection [9].

In 2006, the country attractiveness index for clinical trials was developed based on patient availability, cost efficiency, relevant expertise, regulatory conditions and national infrastructures and it considered USA, China and India as the most attractive locations [9].

For China to be on the top of this ranking (after USA), several factors were taken into account: the vast patient pool and large infrastructure of the hospitals, the large number of health professionals and their low salaries. India comes in second because it offers vast population, a growing market, the capabilities and experience of the country's scientists, English as primary language and the incentive to promote local pharmaceutical companies and attract foreign firms [9]. Emerging countries are attracting clinical trials due to low costs and the availability of a skilled R&D workforce and of large patient population [6].

However, there are many risks in low-cost countries that companies have to consider and that make pharmaceuticals think before choosing one of these countries. They have to: protect intellectual property, know the regulatory requirements and learn the ethnicity and understand cultural differences (that varies widely from country to country) [9].

To better understand how these parameters have been affected the clinical trials, we can see in the Table 1 and Figure 14 the actual number of clinical trials in Europe and in other continents. The data below were obtained by a research carried out on web site clinicaltrials.gov. Making an advanced search with only one criterion, the time of first received. So, for the year 2010 the timeline was put between 01/01/2010 and 12/01/2012. The same strategy was followed for 2011 and 2012. To 2013 the timeline between 01/01/2013 to 06/30/2013 was considered.

Table 1: Number of CT approved in the World (2010-2012), registered at clinicaltrials.gov. Adapted from source [30].

	Canada	USA	South America	Europe	Africa	North Asia	Middle East	South Asia	East Asia	Pacifica
2010	1240	7310	674	5477	396	370	872	414	1926	439
2011	1254	7305	739	5748	391	390	864	324	2176	444
2012	1350	7550	694	6045	446	329	826	361	2375	415

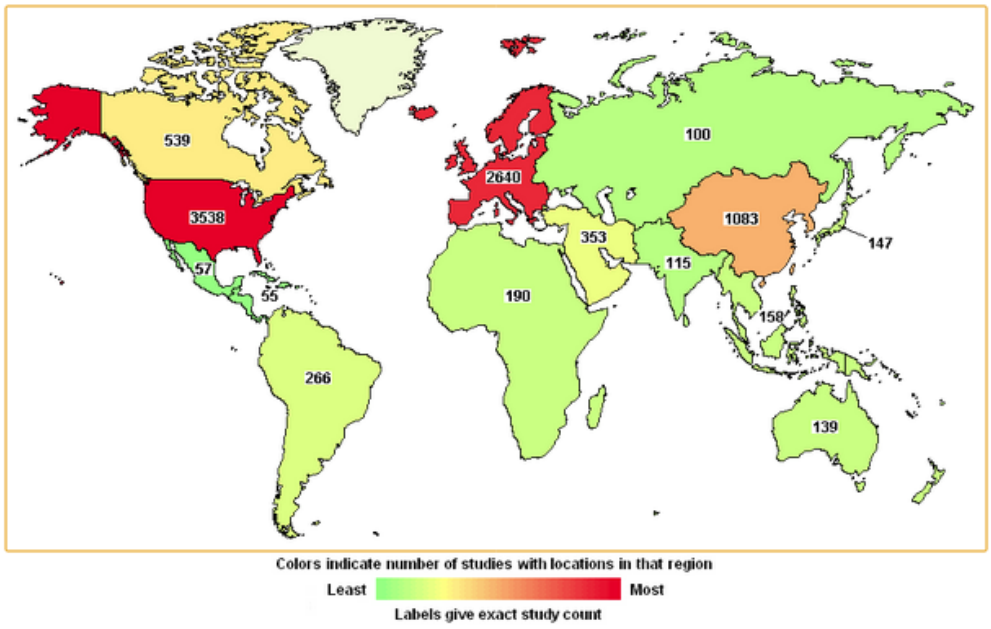

Figure 14: Clinical trials in the World (1st semester 2013). Representative graphic of the number of clinical trials distributed by the World in first half of 2013, registered at clinicaltrials.gov. Reproduced from source [30].

The numbers represent a small variation in CT number performed in Europe. Despite the R&D investment decline, graphics represent a slight increase in CT numbers. However, this can be result of an improvement of data coverage by clinicaltrials.gov and can be a fictitious increase [31].

III.II. Portugal vs Other Countries

After analyzing the clinical trials trend in Europe, it is important to check the Portuguese situation. If, by 2011, Europe had a small average market growth of 2.6%, Portugal hadn't seen any growth and the evolution was negative. As can be seen on Table 2, on the top 50 of market growth from 2007 to 2011, Portugal appeared in 44th with a average market growth of -3.97% behind countries like Austria, Belgium and Czech Republic whose markets grew of 27.19%, 18.61% and -3.44%, respectively [31].

Table 2: Portugal market growth on clinical trials among the top 50 countries (2007-2011). Reproduced from source [31].

Rank	Country	Clinical Trials	Market Share	Region	Market Growth
1	Singapura	777	0,52%	Ásia	138,48%
2	Hong Kong	596	0,40%	Ásia	98,46%
3	Israel	2857	1,90%	Médio Oriente	93,02%
4	Porto Rico	1135	0,75%	América Latina	92,15%
5	Suíça	2196	1,46%	Europa Ocidental	88,06%
6	Tailândia	844	0,56%	Ásia	59,98%
7	Coreia do Sul	2328	1,54%	Ásia	52,46%
8	Croácia	383	0,25%	Europa de Leste	51,36%
9	Noruega	1515	1,01%	Europa Ocidental	50,42%
10	Estónia	368	0,24%	Europa de Leste	48,04%
11	Dinamarca	2543	1,69%	Europa Ocidental	47,00%
21	Bélgica	3054	2,03%	Europa Ocidental	18,61%
22	Eslováquia	692	0,46%	Europa de Leste	17,67%
23	Filipinas	447	0,30%	América Latina	16,09%
24	Reino Unido	5305	3,52%	Europa Ocidental	15,54%
25	Brasil	2147	1,42%	América Latina	14,14%
39	Itália	4024	2,67%	Europa Ocidental	-0,38%
40	México	1329	0,88%	América Latina	-0,68%
41	França	6137	4,07%	Europa Ocidental	-1,77%
42	Polónia	2178	1,44%	Europa de Leste	-3,23%
43	República Checa	1487	0,99%	Europa de Leste	-3,44%
44	Portugal	664	0,44%	Europa Ocidental	-3,97%
45	Espanha	3549	2,35%	Europa Ocidental	-5,31%
46	Alemanha	7144	4,74%	Europa Ocidental	-5,62%
47	Argentina	1123	0,74%	América Latina	-8,50%
48	EUA	52832	35,05%	América do Norte	-9,34%
49	Rússia	1559	1,03%	Europa de Leste	-10,35%
50	Japão	1773	1,18%	Ásia	-18,81%

If we analyze the top 50 by market share in 2011, Portugal rose from 44th to 39th with a market share of 0.44% [31].

These results reflect the R&D investment. Countries with a strong tradition in R&D investment are the ones that have a big share of GNP (Gross National Product) percentage given to R&D investment and are the ones with higher market growth and market share. Portugal is in the other group of countries with the lower investment in R&D [31].

As a consequence of the lower investment in R&D, the number of clinical trials submitted in Portugal during the period between 2006 and 2009 is lower than the number submitted in other countries like Belgium, as can be easily appreciated in Figure 15 [7].

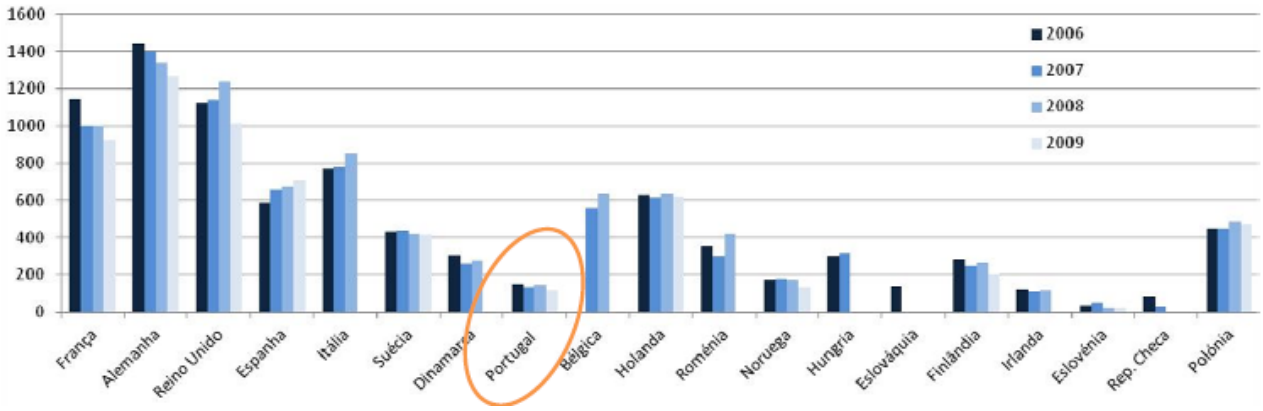

Figure 15: Number of clinical trials in Europe (2006-2009). Reproduced from source [7].

By 2010, the trend was the same and Portugal appears between the countries with the lower rate of clinical trials per million inhabitants. As represented in Figure 16, in 2010 Portugal has the lower ratio of clinical trials per million inhabitants.

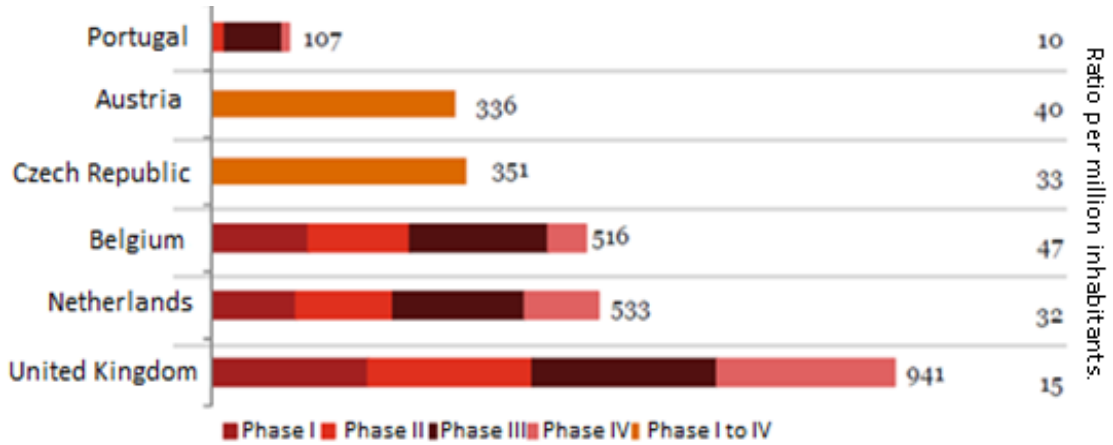

Figure 16: Clinical trials in Europe (2010). Representative graphic of the number of clinical trials authorized, per phase, and the ratio per million inhabitants, in 2010. Portugal appears between the countries with the lower rate of clinical trials per million inhabitants. Adapted from source [8].

Along with a low number of clinical trials, comes lower investment from sponsors. Table 3 compares the active clinical trials, number of sites, number of patients and the total investment in Portugal, Austria, Belgium and Czech Republic. Comparing Portugal with these similar countries, in terms of number of inhabitants, the difference of investment is evident. Belgium captures approximately more €136 millions than Portugal and Czech Republic more €173 millions [7].

Table 3: Active clinical trials (2009). Number of active clinical trials and its investment in 2009. Adapted from source [7].

Countries	Active Clinical Trials	Number of Sites (Planned)	Number of Patients (Planned)	Investment (Million €)
Portugal	147	461	3917	58.755
Austria	188	596	6502	97.530
Belgium	328	1024	12996	194.940
Czech Republic	218	967	15433	231.495

This difference of investment is a consequence of the different number of planned patients, which is the lowers in Portugal. Figure 17 and Figure 18 can help to better understand the situation of Portugal. The number of participants in clinical trials and the number of clinical trials and patients per site is low in Portugal, reflecting the difficulty to recruit patients for clinical trials.

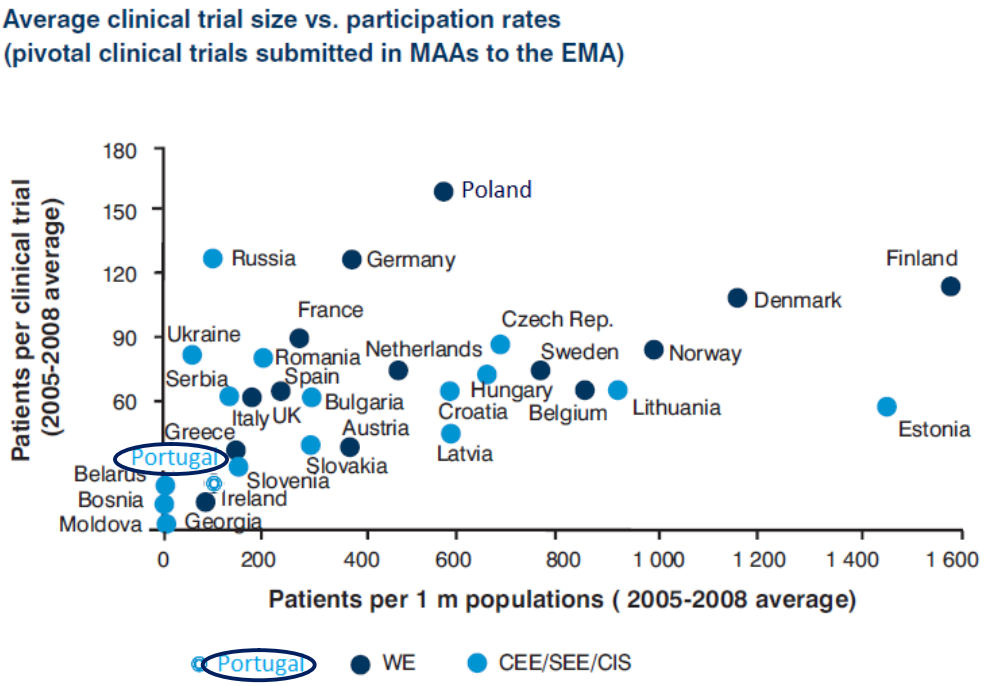

Figure 17: Patients per clinical trial in Europe (2005-2008). Adapted from source [5].

Portugal has fewer patients per clinical trial and fewer patients per site than Belgium, Austria and Czech Republic.

Portugal has also a reduced number of CT per sites, clearly below that of other Western European countries. As a consequence, the number of patients included in clinical trials per site is lower.

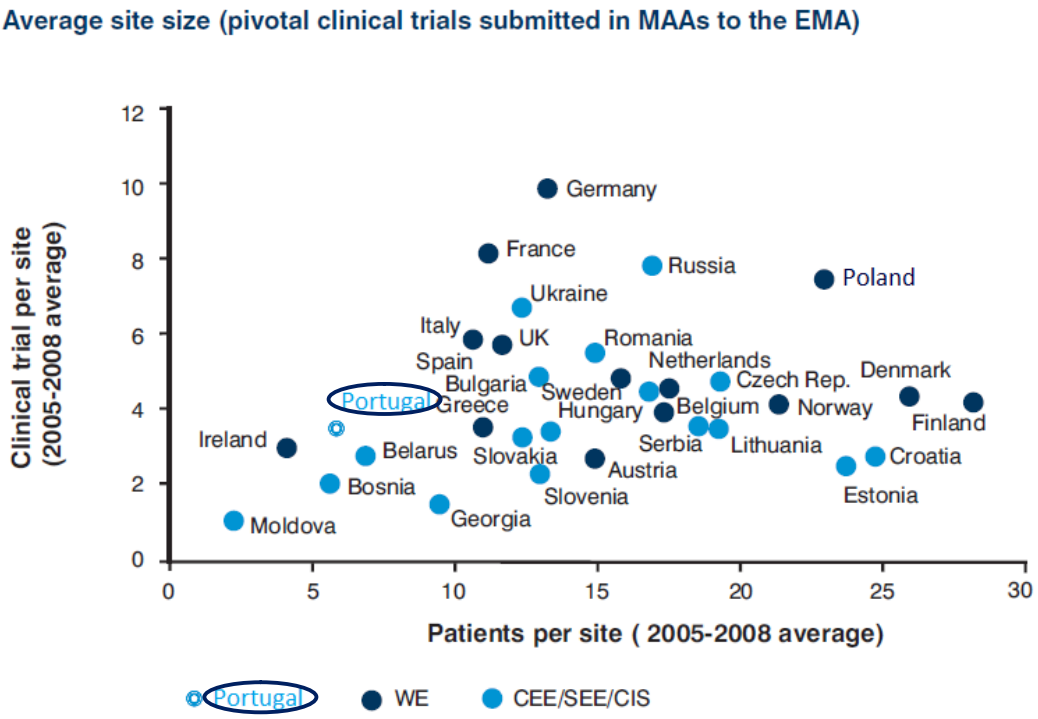

Figure 18: CT and patients per site in Europe (2005-2008). Adapted from source [5].

Another difference between Portugal and other countries is the ratio between clinical trials promoted by pharmaceutical industry and by the investigator initiative. Countries like Spain and United Kingdom have a high number of "academic trials" that represents even ¼ of whole clinical trials, in 2010 [8].

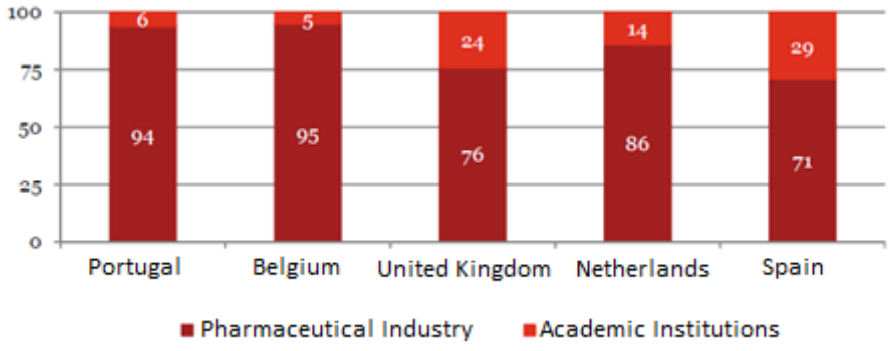

Figure 19: Proportion of CT by type of sponsor (2010). (%) Adapted from source [8].

There are more factors that can be compared in order to frame the main differences between Portugal and some European countries with similar population and to identify the major reasons that make them more attractive than Portugal in clinical research.

Table 4: Variation factors between Portugal and similar countries. Adapted from source [8].

Countries	Portugal	Austria	Belgium	Czech Republic
Time to regulatory approval. (days)	60	35	15-28	60
Policy and Strategy		- Organization dedicated exclusively to clinical research. - Financing funds to research.	- One non-profit cluster that interacts with various stakeholders promoting a favourable environment to clinical trials (Healthcare Belgium).	- Funding and incentives for research projects of academic initiative.
Regulation and Legislation	- Templates for some documents such as informed consent (in PNEC). - Bureaucracy and non standardized procedures with many variations depending on the institutions. The obligation of the approval by CNPD.	- Models of informed consent and guidelines in order to get standardization.	- Clear guidelines and standardization to increase transparency. - More uniformity to reduce administrative burdens for companies.	
Organization and infrastructure	- Lacks in the quality of infrastructures mainly for phase 1 (that require internment).	- Centres of excellence, groups of clinical research and groups to help patients.	- Qualified centres dedicated to clinical research.	- Centres of excellence specialized in therapeutic areas.
Technology and Information	- One platform to submit the amendments and changes in study authorization and follows the status of the request. Clear instructions for companies, electronic submission of documents and monitoring of the status of the request.	- One platform that helps and facilitates the recruitment and the divulgation of clinical trials.	- One platform between industry and patients to helps in the access to information.	- Provision of information on clinical trials in internet. - Implementation of system “one stop shop” that centralized the submission of clinical trial.
Incentives, Training and Career	- No valuing the research career. - Few people are exclusively dedicated to clinical trials and clinical research.	- Training programs and certification of investigators.		- Fair remuneration to the investigators.

Table 5 and Figure 20 give a global vision of the number of clinical trials carried out in Portugal and in other countries of Europe, from 2010 until the first semester of 2013.

Table 5: Number of CT approved in Europe (2010-2012), registered at clinicaltrials.gov. Adapted from source [30].

	Portugal	Spain	French	Belgium	Austria	Czech Republic	Germany	United Kingdom
2010	100	689	1200	582	346	288	1385	1032
2011	87	778	1244	578	360	299	1434	988
2012	114	757	1290	540	320	253	1244	1060

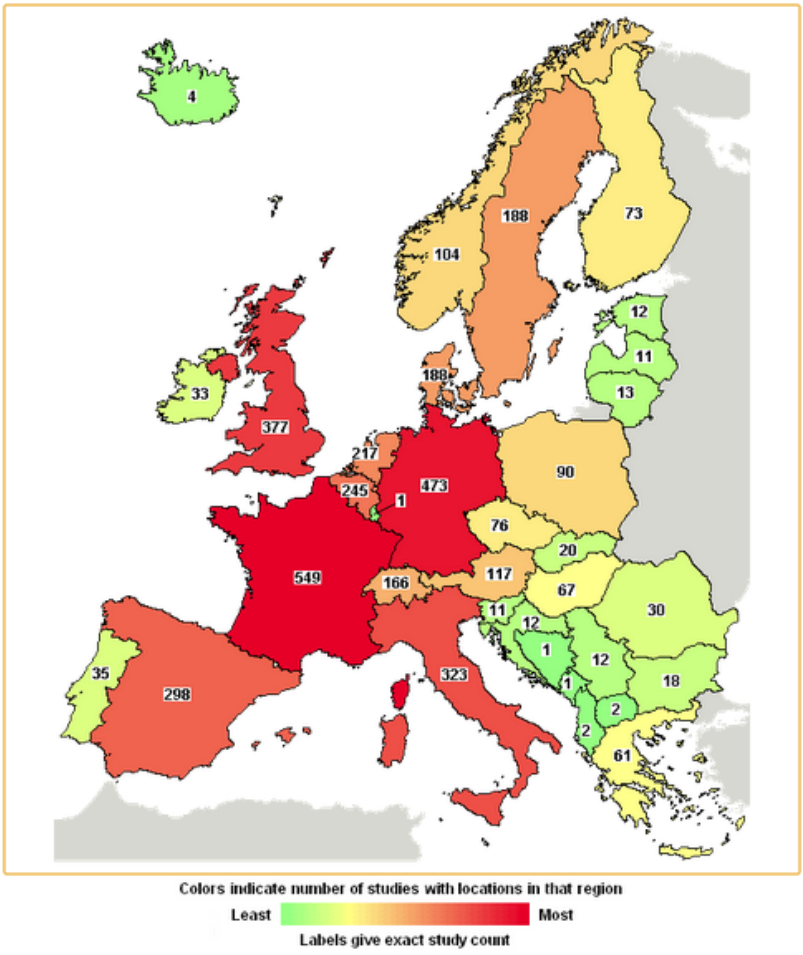

Figure 20: Number of CT in Europe (1st semester 2013). Reproduced from source [30].

If the Portuguese trend continues in the 2nd semester of 2013 we will have, in the end of 2013, a very low CT number, approximately 70 CT, being 2013 the year with lower number of CT approved, since 2006.

The decline in the number of clinical trials has had a great impact in all stakeholders and brings large losses for Portugal. We should emphasize the loss of jobs, expertise personnel, innovation and budget, the closure of local clinical operations departments of pharmaceutical companies and of research sites, fewer publications and decreased access to innovative treatments [6].

III.III. Portuguese Overview

Since INFARMED is the authority responsible for the approval and the authorization of clinical trials, it should be interesting to analyze its available data since 2006 to 2012, in order to understand the trend on the number of clinical trials submitted and approved in Portugal (Figure 21).

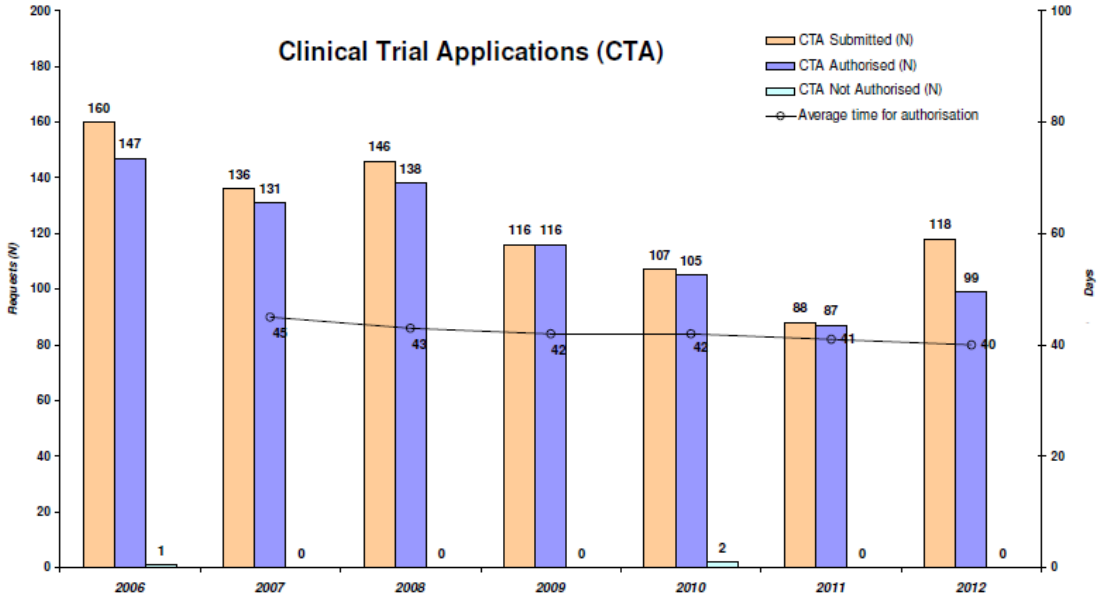

Figure 21: Clinical trials applications submitted and approved by INFARMED (2006-2012). Reproduced from source [32].

As show in Figure 22, it is on late development (phase III) that more investment appears.

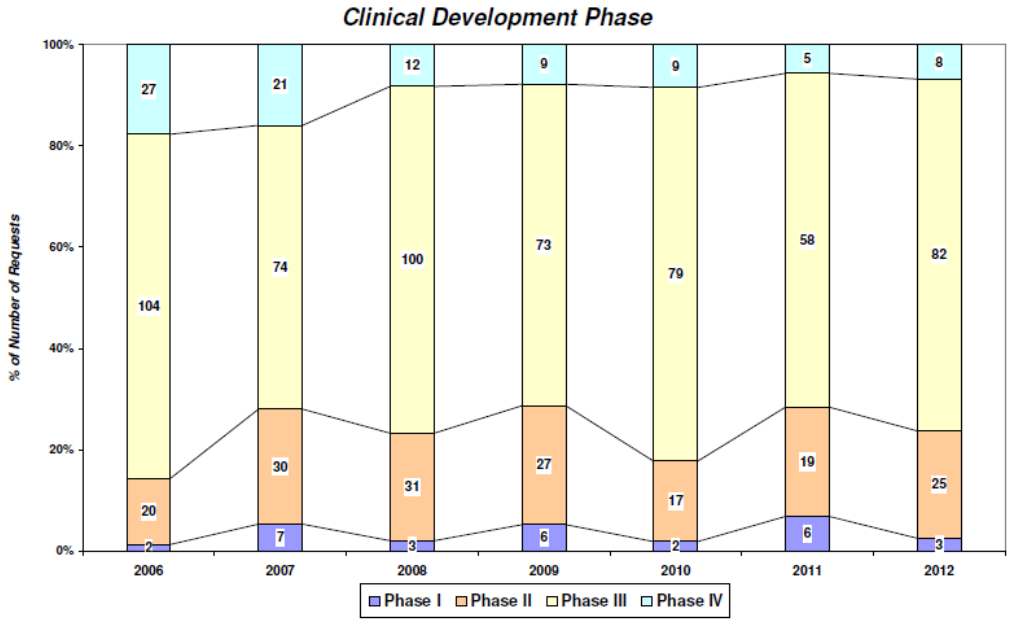

Figure 22: Clinical development phase (2006-2012). Number of submitted and valid clinical trials of each phase, between 2006 and 2012. In every year it is on phase III that more investment appears. Reproduced from source [32].

The analysis by type of medicines (tested in Portugal since 2006) shows that chemistry origin is still the most studied and the percentage of biotechnological ones has not changed significantly (Figure 23 and Table 10) [32].

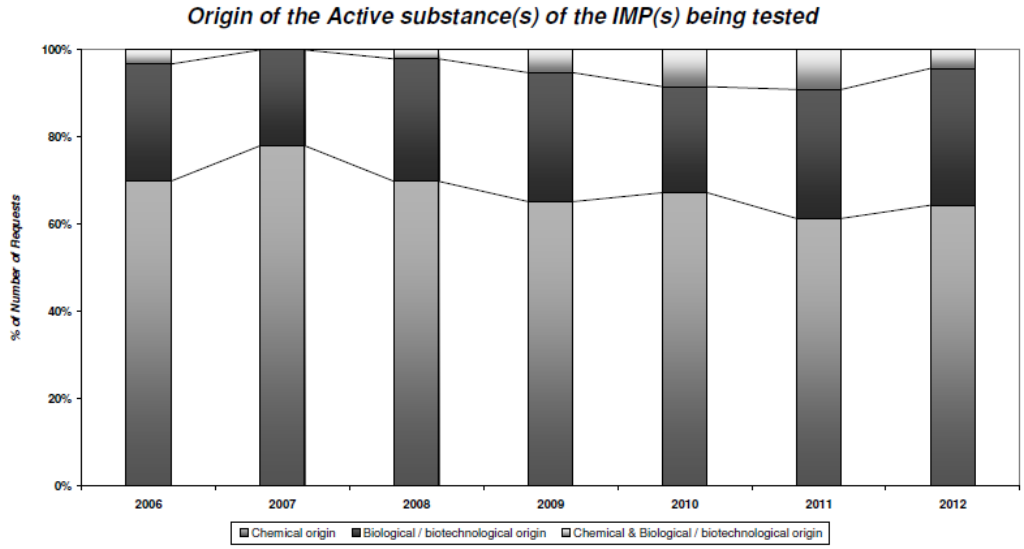

Figure 23: Type of the active substances tested in CT performed in Portugal (2006-2012). Reproduced from source [32].

It is also interesting, after knowing how many clinical trials were performed and of which phases and origin they come from, to understand who are the big investors in clinical research. Figure 24 represents the two type of sponsors that have been coexisting in Portugal: Pharmaceutical Industry and Academical Researchers. However, the number of investigator-driven clinical trials has been much smaller than the clinical trials sponsored by the Industry (95% versus 5%- Table 11) [32].

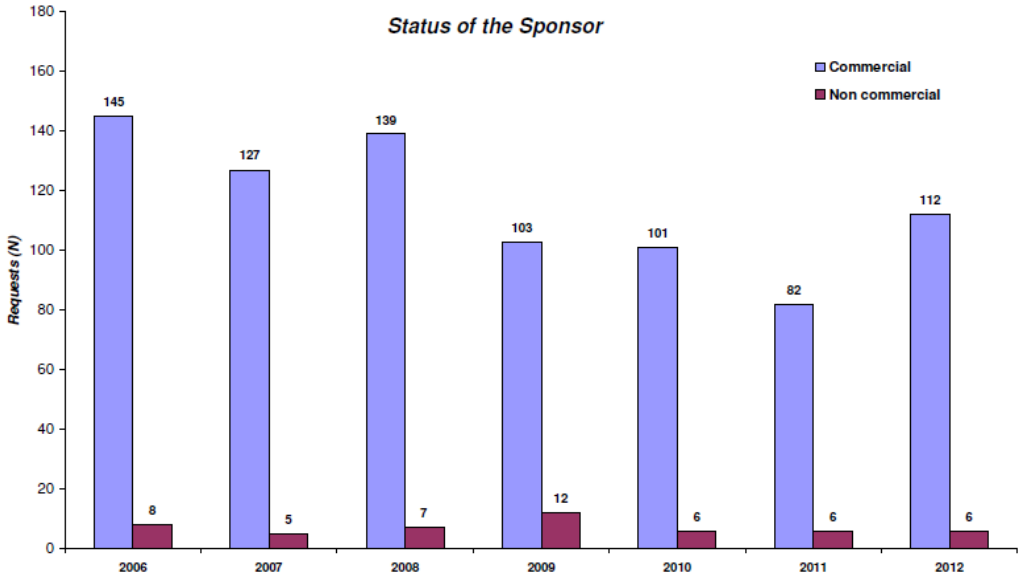

Figure 24: Number of study applications submitted to INFARMED by type of sponsor (2006-2012). Reproduced from source [32].

INFARMED shared information of the number of requests for substantial amendments of clinical trials approved and the average time to evaluate these changes. There has been an improvement in the number of days necessary to answer the request and a significant increase on the number of answers that have been given on the established time. Since 2006 this number increased from 60% in 2006 to 99% in 2012 (Figure 25 and Table 12) [32].

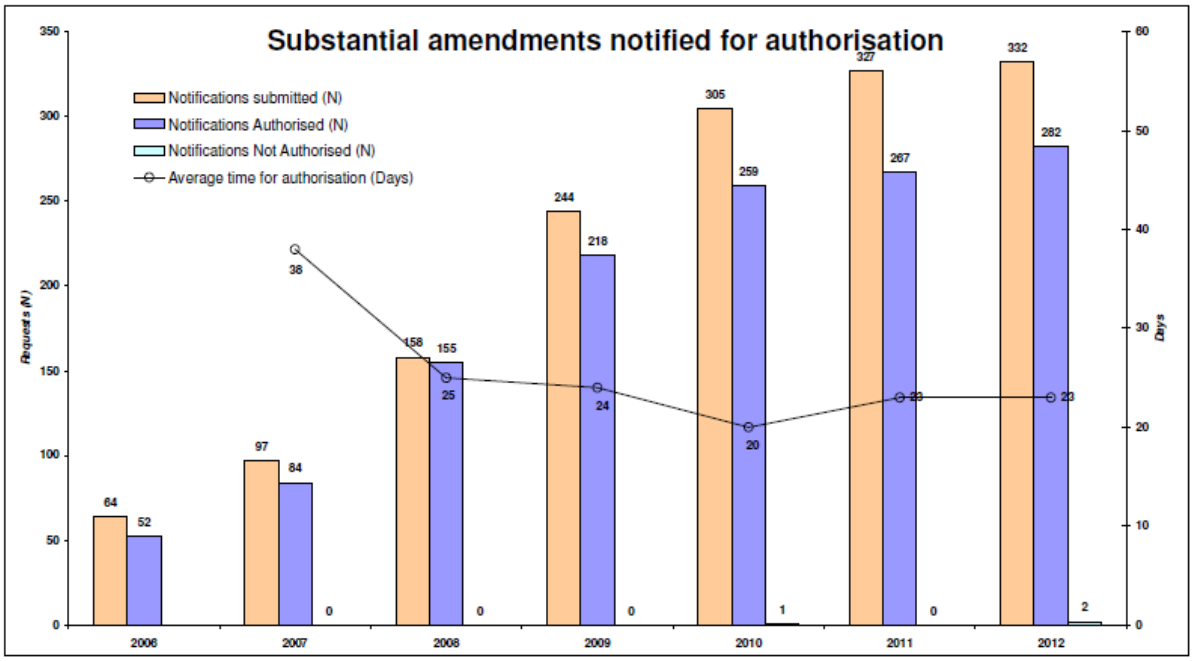

Figure 25: Substantial amendments notified for authorization (2006-2012). Number of submitted, authorized and rejected requests for substantial changes of approved clinical trials, between 2006 and 2012, and average time of decision in the same period. Reproduced from source [32].

Once clinical trials are also submitted to approval by CEIC, CEIC data for the same period (2006 to 2012) were analysed.

Figure 26 displays the number of notifications submitted, favourable and unfavourable opinions, notifications invalidates administratively and the average time for decision.

As expected, the number of requests for CT approval by CEIC follows the same trend of the number of CT applications to INFARMED. We could verify a decrease in number from 2006 to 2011. Only in 2008 and 2012 can be seen a slight increase. The average time for the transmission of the CEIC opinion and approval also decreased, since 2007. In 2007 was 66.9 days and in 2012 was 42.3 days [33].

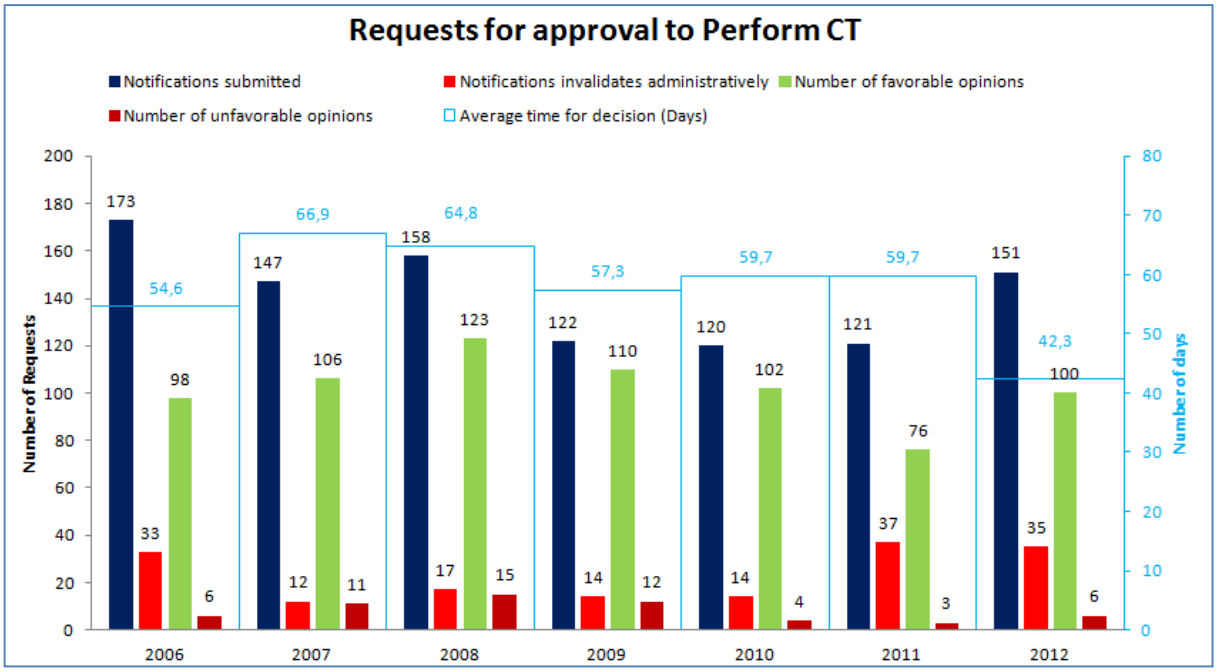

Figure 26: Requests for approval of clinical trials to CEIC (2006-2012). Number of requests invalidated administratively, number of favourable and unfavourable opinions and average time of decision, in the same period. Adapted from source [33].

Regarding requests for opinion, to perform substantial CT amendments, Figure 27 shows an increase of the requests. This follows the same trend of INFARMED's numbers. Related to the average time to answer the request there has been a decrease in the number of days that was very significant for CEIC. In 2006 CEIC took on average of 74.1 days to respond. In 2012 CEIC already responded in 31 days. Despite the same tendency of numbers, between CEIC and INFARMED, the CEIC had always a higher number of requests to important changes than INFARMED [33].

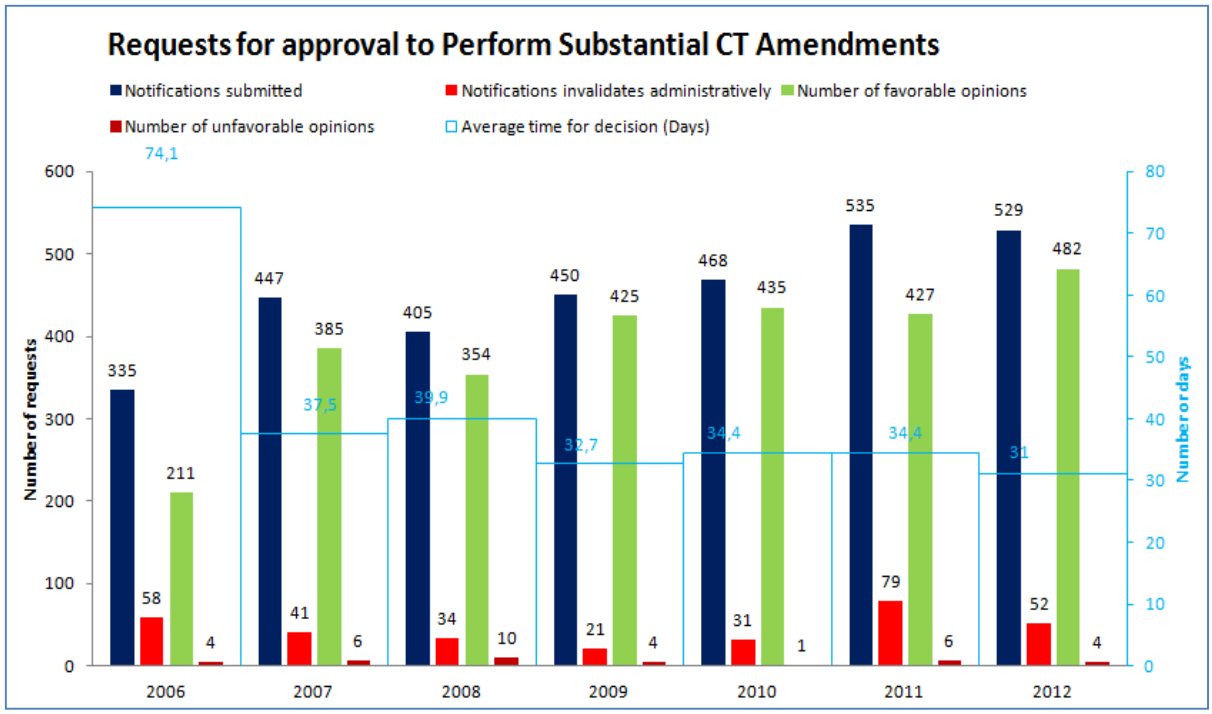

Figure 27: Requests for approval of substantial clinical trials amendments by CEIC (2006-2012). Number of requests invalidated administratively, number of favourable and unfavourable opinions and average time of decision in the same period. Adapted from source [33].

It is important to note that the approval time by CEIC is also affected by the time that sponsor takes to answer to the questions and doubts of CEIC. When CEIC requires additional information from sponsors, they have to study and formulate their answer and this take some time. After that, CEIC has to review the answers. As can be seen in Table 6, sometimes sponsors take a long time to answer.

Table 6: Average time of sponsors answers to the request for additional information by CEIC (2011-2012). Time 0.0 means that the answers were given in one day. Adapted from source [33].

Answers to Additional Information	***To Perform CT (days)***			***Perform Substantial CT Amendments (days)***		
	Average response time	Minimum	Maximum	Average response time	Minimum	Maximum
2011	24.0	1.0	128.0	31.0	1.0	173.0
2012	21.6	0.0	238.0	28.1	1.0	102.0

In Portugal, CNPD must also give the authorization to the clinical trial and the data treatment. Table 7 displays the number of authorized clinical trials by CNPD.

It wasn't possible to access the number of notifications submitted. However, in general, all requests are accepted by CNPD. Sometimes what can occur is a partial authorization. In these cases CNPD doesn't accept the treatment of some data, like racial data, and asks to change the protocol [34].

CNPD numbers are different from the notifications submitted to INFARMED and CEIC. Generally the notifications authorized by CNPD are fewer than INFARMED and CEIC. Despite this difference, the trend is similar. The difference is only noticed in 2011 where CNPD had a slight increase of notifications in contrast to INFARMED and CEIC decrease.

Table 7: Requests to perform clinical trials to CNPD (2006-2012). Adapted from source [34].

CNPD	***2006***	***2007***	***2008***	***2009***	***2010***	***2011***	***2012***
Notifications Authorized (N)	36	91	169	119	98	109	139

Related to average time for the authorization to treat clinical trial data, CNPD hasn't got these data available per year. So, it isn't possible to evaluate the variation and if there has been a decrease in time. However, during my conversation, it was possible to identify that the time for approval varies with the complexity of the clinical trial and also with the necessity of CNPD to require more information or request changes. In this case, the time that sponsors take to answer also has influence in the CNPD authorization time [34].

Despite these variations, generally, CNPD takes in average two months to respond [34].

In Figure 28, the average time between the submission of the request to initial approval and the reception of the consent from the last regulatory entity can be seen, time that exclude the average time of approval by the administrations board of clinical trial sites [8].

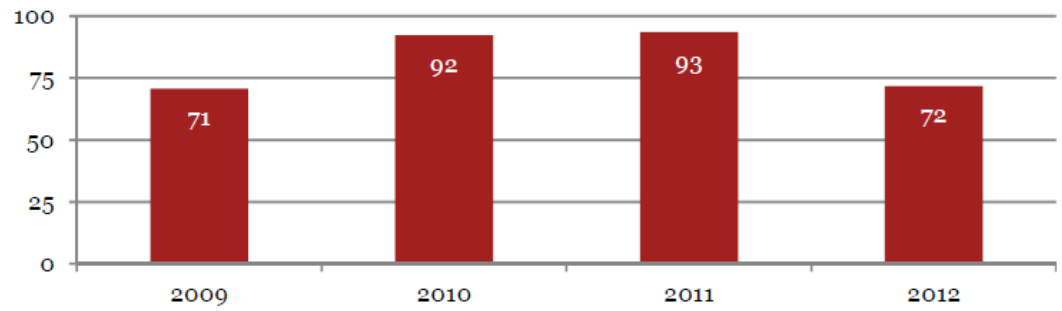

Figure 28: Time of approval by all regulatory authorities, in Portugal (2009-2012). The average time (days) between the submission of the request to initial approval and the reception of the consent from the last regulatory entity, in Portugal. In these numbers are excluded CT whose approval is pending and the average time of approval by the administrations boards of clinical trial sites. Reproduced from source [8].

The previous graphic only considers the average time since the submission of the request to the reception of the consent from the last regulatory entity. If the whole approval process was considered, taking into account also the approval time by sites, the real time of clinical trial approval, in Portugal, is higher than 6 months [8].

It is also important to analyze the investment in clinical trials in Portugal. APIFARMA studied the potential of investment wasted in Portugal. An analysis of 443 clinical trials, conducted from 2007 to 2011, compared how much money was planned to be invested in Portugal versus the money that was actually invested (Table 8) [7].

Table 8: Planned versus real investment (2007-2011). Total of planed investment versus the actually investment in 443 clinical trials conducted in Portugal between 2007 and 2011. Adapted from source [7].

Therapeutic Areas	No. of Studies	Avg. Investment /per patient (€)	Planned Patients	Included Patients	Total investment Planned Patients (€)	Total investment Included Patients (€)
Angiologia	20	4 910	214	318	1 050 643	1 561 236
Cardiologia	75	5 997	787	440	4 719 639	2 638 680
Dor	7	5 549	45	10	249 705	55 490
Endocrinologia e nutrição	18	6 121	109	65	667 189	397 865
Gastroenterologia	19	18 366	157	93	2 883 462	1 708 038
Ginecologia	3	2 594	27	14	70 038	36 316
Hematologia	4	68 520	30	15	2 055 600	1 027 800
Infecciologia	44	20 749	186	173	3 859 314	3 589 577
Medicina Interna	10	14 246	60	27	854 760	384 642
Nefrologia	17	10 816	121	108	1 308 736	1 168 128
Neurologia	54	10 928	753	421	8 228 784	4 600 688
Oftalmologia	17	4 066	172	97	699 352	394 402
Oncologia	50	31 733	276	181	8 758 308	5 743 673
Pneumologia	29	14 585	203	161	2 960 755	2 348 185
Psiquiatria	31	5 537	179	150	991 123	830 550
Reumatologia	11	14 862	56	32	832 272	475 584
Transplante	6	15 780	32	10	504 960	157 800
Urologia	18	4 544	186	144	845 184	654 336
Vacinas	10	3 589	87	30	312 243	107 670
Total	**443**	**13 868**	**3 680**	**2 489**	**41 852 067**	**27 880 660**

For areas like Cardiology and Neurology, the actual investment was approximately 50% of the planned investment. Globally, from 2007 to 2011, Portugal lost approximately €14 millions of the planned investment. The number of non-included patients was 1191, which corresponds to 32.4% of the planned number of patients. Portugal only included 70% of patients initially planned [7].

This is a consequence of a decrease on the number of new patients recruited for CT that have been noticed, with an exception for the year 2011 (Figure 29) [8].

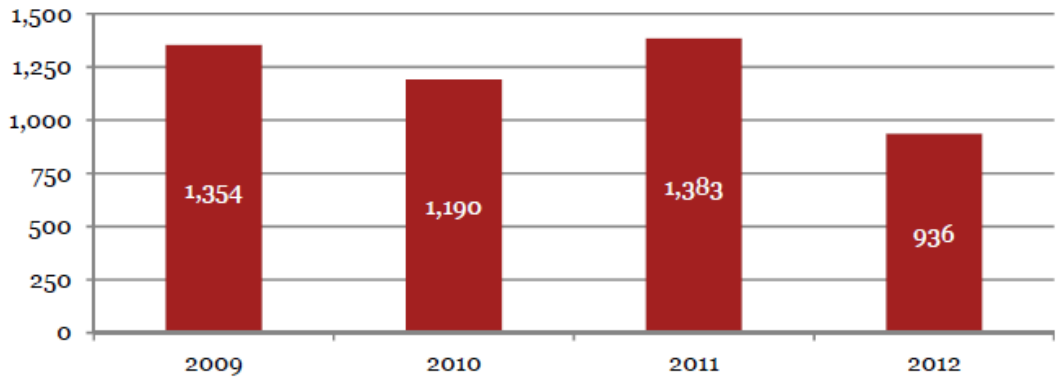

Figure 29: New patients recruited in Portugal (2009-2012). With exception for the year 2011, between 2009 and 2012, the recruitment of new patients has been decreased. In 2012 only 936 new patients were recruited. Reproduced from source [8].

The total investment in 2012, in Portugal, was €36 millions that correspond to €3.6 per capita. In EU, the investment was €20,000 millions. This corresponds to €40 per capita. If Portugal would be in the EU average the investment would be about €400 millions instead of €36 millions [29].

The economic value of clinical trials has a very relevant impact on Portuguese economy. In 2012 the market value was €36 millions, with a direct gross value added of €21 millions and €7.5 millions of tax revenues. The value of exports resulting from the clinical trials rose to €33 millions, which contributed for less public spending, saving €3.5 millions to the State and we also had, in 2012, 1086 jobs dedicated to clinical trials. The global impact on Portuguese economy can be evaluated using GNP multipliers. For the clinical trials area, this multiplier is €1.98, which means that every €1 investment generated in clinical trials activity provides a return of €1.98 for the general Portuguese economy. This puts clinical trials on the top 10 for the activities with better return (Figure 30)[8].

Multiplying the factor of multiplication for clinical trials with the market value of this activity we obtain the total impact of clinical trials in Portuguese economy, which was €71 millions in 2012 [8].

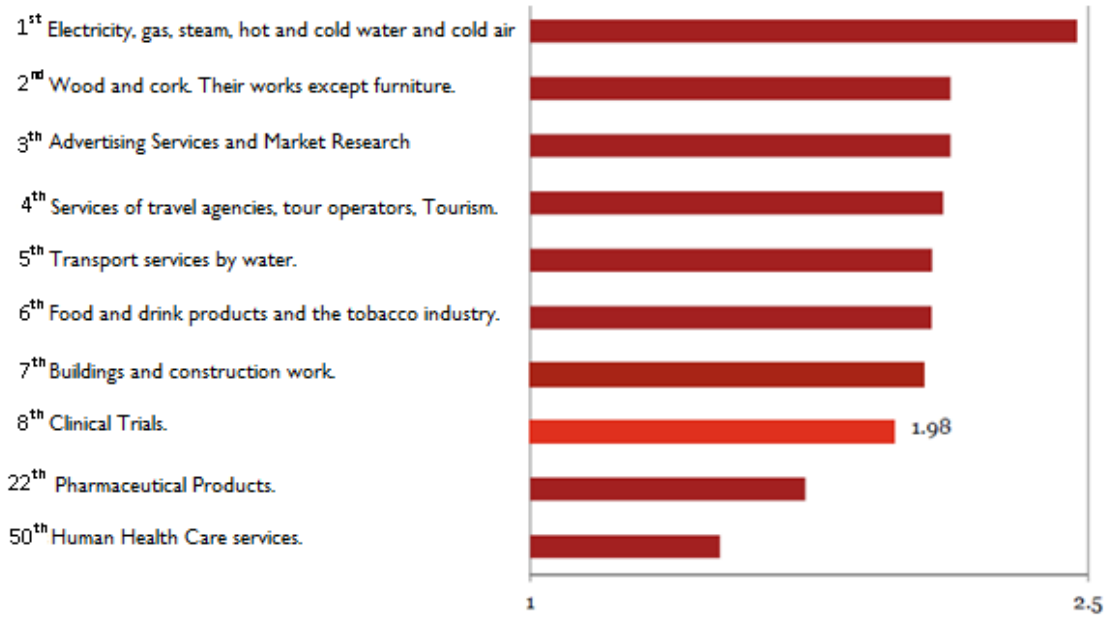

Figure 30: GNP multipliers. GNP multipliers for each Portuguese activity sector. For the clinical trials area, this multiplier is €1.98, which means that every €1 investment generated in clinical trials activity provides a return of €1.98 for the general Portuguese economy. Adapted from source [8].

Another issue that can be interesting to analyse is the distribution of clinical trials per site and per sponsor, in Portugal.

Analysing the CT per sites in Table 9, we observe that 30% of the clinical trials conducted in Portugal are concentrated in two big sites. Between 2006 and 2011, from 22 centres that performed more than 10 clinical trials, only 6 are responsible for performing 609 clinical trials of the 943 (the total number of CT considered for this period), that corresponds to approximately 65% [35]. The clinical trials performed in primary health care units are greatly reduced [8].

Table 9: Table of the distribution of clinical trials per site (2006-2011). (It was considering only sites that performed more than 10 clinical trials). Adapted from source [35].

Sites/ Researchers	No. CT
CENTRO HOSPITALAR E UNIVERSITÁRIO DE COIMBRA, (CHUC)	158
CENTRO HOSPITALAR DE LISBOA NORTE (CHLN)	135
CENTRO HOSPITALAR PORTO, E.P.E. - HOSPITAL DE SÃO JOÃO	98
CENTRO HOSPITALAR DE LISBOA CENTRAL (CHLC)	96
INSTITUTO PORTUGUÊS DE ONCOLOGIA DE PORTO FRANCISCO GENTIL, E.P.E.	61
CENTRO HOSPITALAR DE LISBOA OCIDENTAL (CHLO)	61
INSTITUTO PORTUGUÊS DE ONCOLOGIA DE LISBOA, FRANCISCO GENTIL, E.P.E.	48
HOSPITAL PROFESSOR DOUTOR FERNANDO FONSECA, EPE	46
CENTRO HOSPITALAR DO PORTO, E.P.E. - HOSPITAL GERAL DE SANTO ANTÓNIO	43
AIBILI - ASSOCIAÇÃO PARA A INVESTIGAÇÃO BIOMÉDICA E INOVAÇÃO EM LUZ E IMAGEM	25
HOSPITAL INFANTE DOM PEDRO, EPE - AVEIRO	24
HOSPITAL GARCIA DE ORTA, EPE	23
INSTITUTO PORTUGUÊS DE ONCOLOGIA DE COIMBRA FRANCISCO GENTIL, E.P.E.	20
CENTRO HOSPITALAR DE VILA NOVA DE GAIA/ESPINHO, EPE	14
CENTRO HOSPITALAR DE TRÁS-OS MONTES E ALTO DOURO, EPE - HOSPITAL SÃO PEDRO DE VILA REAL	13
HOSPITAL DA LUZ, SA	13
HOSPITAL DE FARO, EPE	12
HOSPITAL DO ESPÍRITO SANTO ÉVORA, EPE	12
CHEDV, EPE - HOSPITAL S. SEBASTIÃO	11
CENTRO HOSPITALAR DE SETÚBAL - HOSPITAL DE SÃO BERNARDO	10
HOSPITAL JOAQUIM URBANO	10
HOSPITAL DE SÃO MARCOS BRAGA	10

Analysing the most recent data about the distribution of CT per Portuguese localities (research carried out on web sites www.centerwatch.com, clinicaltrials.gov and clinicaltrialsregister.eu., in 13 August 2013, by Pedro Silva) it can be verified that there is a concentration of CT in Oporto, Lisbon, Coimbra and Almada. As shown Figure 31, all other localities are performing, each one, less than 10 CT and the majority only one or two [36].

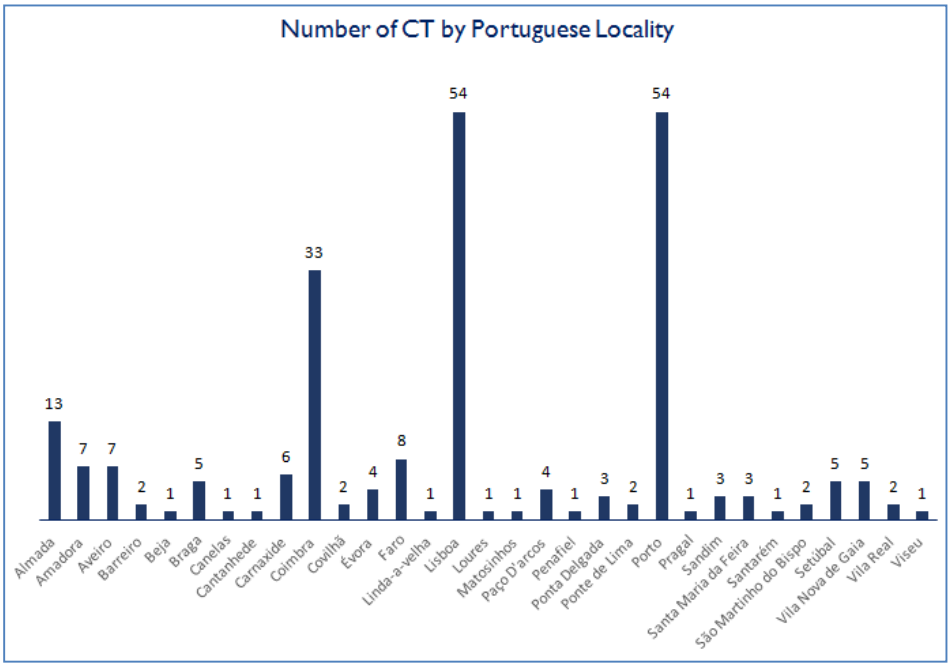

Figure 31: Number of CT by Portuguese locality (August 2013). Graphic representation of the distribution of CT per different localities of Portugal. There is a concentration of CT in Oporto, Lisbon, Coimbra and Almada. All other localities only are performing, each one, less than 10 CT and the majority only one or two. These data were updated at 19 August 2013. Adapted from source [36].

The distribution of CT per sponsor can be analysed in Figure 32. In 2012, Portugal had 41% of the whole active CT provided by only 3 companies and 59% of the number of recruited patients concentrated in the same 3 companies [8].

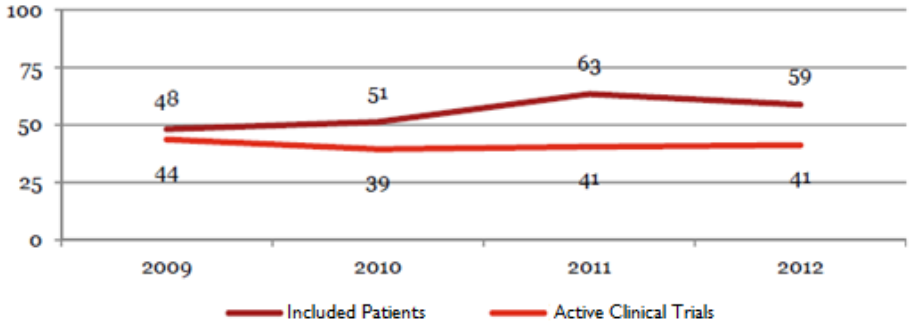

Figure 32: Clinical trials concentration on top 3 companies (2009-2012). Concentration of clinical trials and patients on the top 3 companies, between 2009 and 2012. In 2012, we had 41% of the whole active clinical trials in Portugal provided by only 3 companies and if we analyze the number of patients recruited, the concentration is even higher reaching 59%. Adapted from source [8].

The top sponsors who had the most clinical trials approved by INFARMED in 2012 are: Merck Sharp & Dohme Corp., Janssen-Cilag International NV, Novartis Pharma AG, Boehring Ingelheim, F. Hoffmann-La Roche Ltd., Astellas Pharma Europe B.V., Amgen Inc. and GlaxoSmithKline Research and Development Limited. They are all international companies [32].

Figure 33 shows the sponsors of CT that are being currently perform in Portugal (research carried out on web sites www.centerwatch.com, clinicaltrials.gov and clinicaltrialsregister.eu., in 13 August 2013, by Pedro Silva) [36].

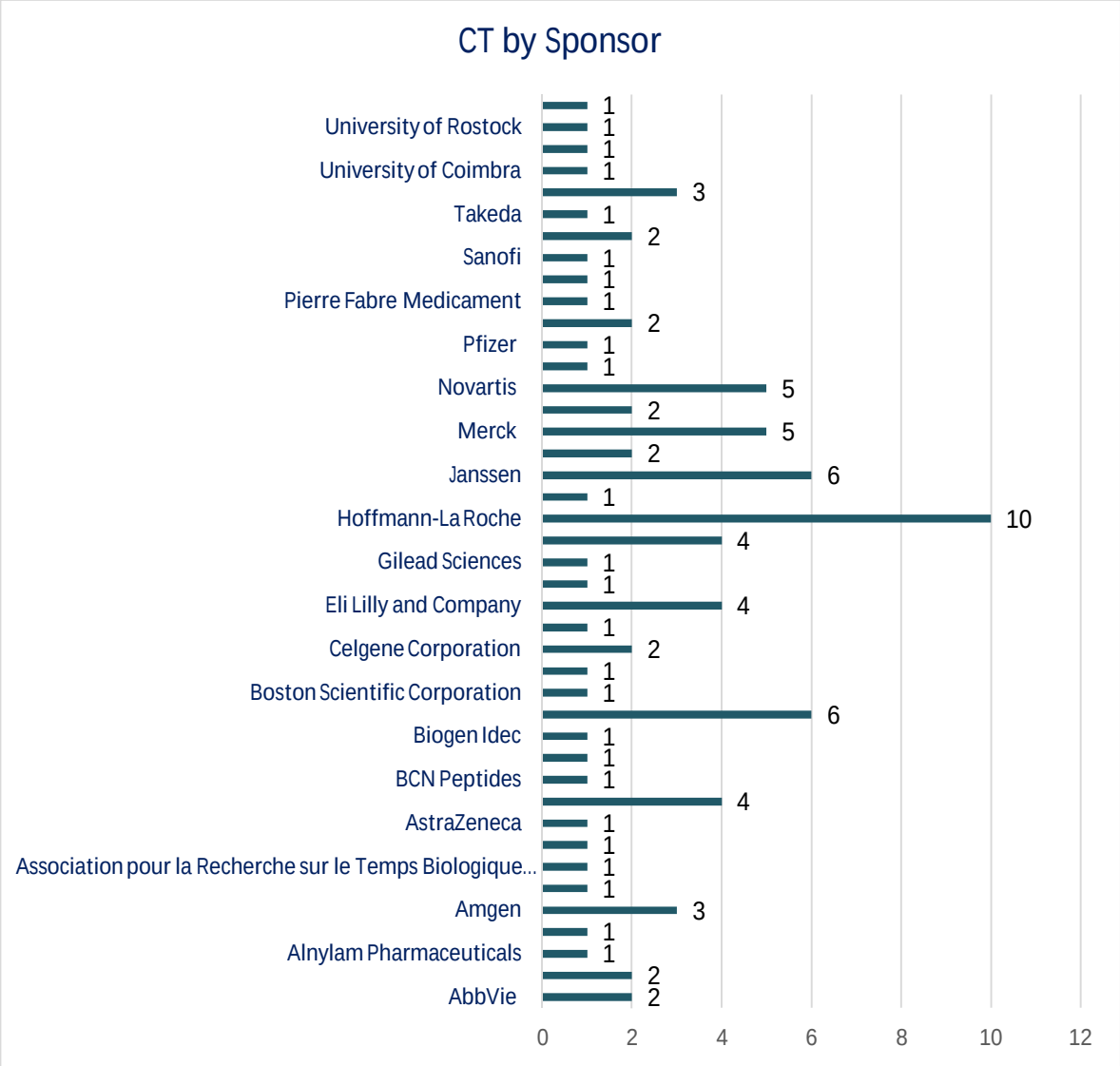

Figure 33: Clinical trials by sponsor (August 2013). Graphic representation of the distribution of CT per sponsors. The sponsor who performed more CT in Portugal is Hoffmann- La Roche with 10 CT. These data were updated at 19 August 2013. Adapted from source [36].

IV. Critical Factors, Perspectives and Challenges of Clinical Trials in Portugal

IV.I. Critical Factors for Portuguese Clinical Trials

Bureaucracy

The Directive 2001/20/EC is considered by many voices as one of the causes for the decrease of the number of clinical trials in Europe (25% from 2007 to 2011) and, consequently, in Portugal [37].

In spite of the fact that this Directive has brought important improvements related with participants safety and ethics, it should be the legislative act of the EU most criticized in the field of pharmaceutical products, by all sectors involved (investigators, industry and participants). The main reason is being a Directive whose transposition for national legislation varied from country to country because the obligation is related to the final result and every country is free to adopt the most appropriate methods to achieve that [38].

The result was an unfavourable regulatory framework for clinical research with direct effects on the costs and feasibility of clinical trials. The consequences were an increase on the costs of clinical trials (the necessary human resources increased a lot, as have the administrative requirements, mainly for non industry sponsors-97%) and an increase of the mean period until the beginning of the clinical trial (in 90%), which reached 152 days. This directive brought an excessive administrative and bureaucratic burden and it does not differentiate the sponsor and the different risk of the different phases of the clinical trial [38].

In order to modify this situation there is a new legislation proposed by the European Commission that will take the form of a Regulation. A Regulation doesn't need transposition and is direct and globally applied in all member states without the involvement of national authorities. This ensures harmonized and standardized procedures and it will propose:

- An authorisation procedure for clinical trials which will allow a fast and through assessment of the application by all MS [37];
- Simplified reporting procedures in order to spare investigators from submitting identical information to various bodies and MS [37];
- More transparency on recruitment participation [37];
- Clear deadlines and a principle of tacit approval to ensure compliance [38];
- Each MS is responsible for defining the organizational structure and internal skills for the evaluation of each authorization request for clinical trials [38];

- Eliminates the requirement imposed by Directive 2001/20/EC related to the existence of the insurance/ compensation for clinical trials where there is no additional risk or when the risk is negligible, in order to reduce costs and administrative burden. (The requirement of this insurance worsened the costs and administrative burden of performing clinical trials by non-commercial sponsors, which have great difficulty in obtaining this coverage) [38];
- The implementation of controls by the European Commission, in MS and other countries, to make sure the rules are being properly supervised and enforced [37].

With this regulation, a more identical application of the legislation will be obtained, reducing the differences between countries. This proposal has been discussed in the European Parliament and it is expected to come into effect in 2016 [37].

In addition to this problem, that is transversal to every MS, Portugal has other bureaucratic problems that make its situation more unfavourable than the other MS.

- Double ethical evaluation.

When directive 2001/20/EC was transposed in Portugal, CEIC was created. As referred in Chapter II, the objective of this creation was to standardize the ethics and makes this authorization independent of the existence of ethics committees in the clinical trials centres. However, even though only one opinion is required by law (opinion by CEIC or Opinion by any CEC designated by CEIC) in Portugal, what usually happens is that the clinical trials sites do not approve the trial without the favourable opinion of their own ethics committee. So, a kind of double ethical evaluation is created, delaying the trial start. The process takes longer when the opinion of different CES is totally different.

- Approval by CNPD.

The Directive 2001/20/EC doesn't require the approval of trials by commissions related with data protection. However, Portuguese legislation created the CNPD that has to be notified by the sponsor and has to give permission to start the clinical trial [23]. To complicate the situation this commission hasn't experts specializing in health area and there isn't a deadline on the CNPD approval. As more agents have to give permission to the sponsor, more complexity in the approval process and more delays occur for the start of clinical trial. It is important to review the role of CNPD. A guideline should be created and would be approved by CNPD of which obeyed the treatment of data and that shouldn't require the approval of CNPD, or alternatively, defining, at least, deadlines for the approval of CNPD [8].

- Specific legal framework for disclosure of clinical trials.

In Portugal there aren't specific laws for the divulgation of clinical trials and it is applied the legal framework for medicines [8]. On "Statute of Medicines" can be found the regulation for public advertising and advertising for health care professionals. The rules for advertising medicines that need medical prescription are very restrictive. The advertising for this type of medicines is limited to health care professionals, through technical publications, and never be accessible to the public [39]. There is a pressing need to provide specific legislation to clinical trials in order to avoid lack of knowledge about ongoing clinical trials and consequently increase the recruitment potential.

These problems along with the approval times by various entities are responsible for delays in the beginning of clinical trials. However, analyzing Figure 34, it is possible to verify that on the top 3 are causes whose responsibility belongs to the sponsors and the centres and not to the authorities and legislations. The negotiations between sponsors and centres, the patient recruitment, drug availability and the protocol design are the main causes for the delay that are listed by Professors Luis Almeida and whose solution will certainly improve clinical research [27].

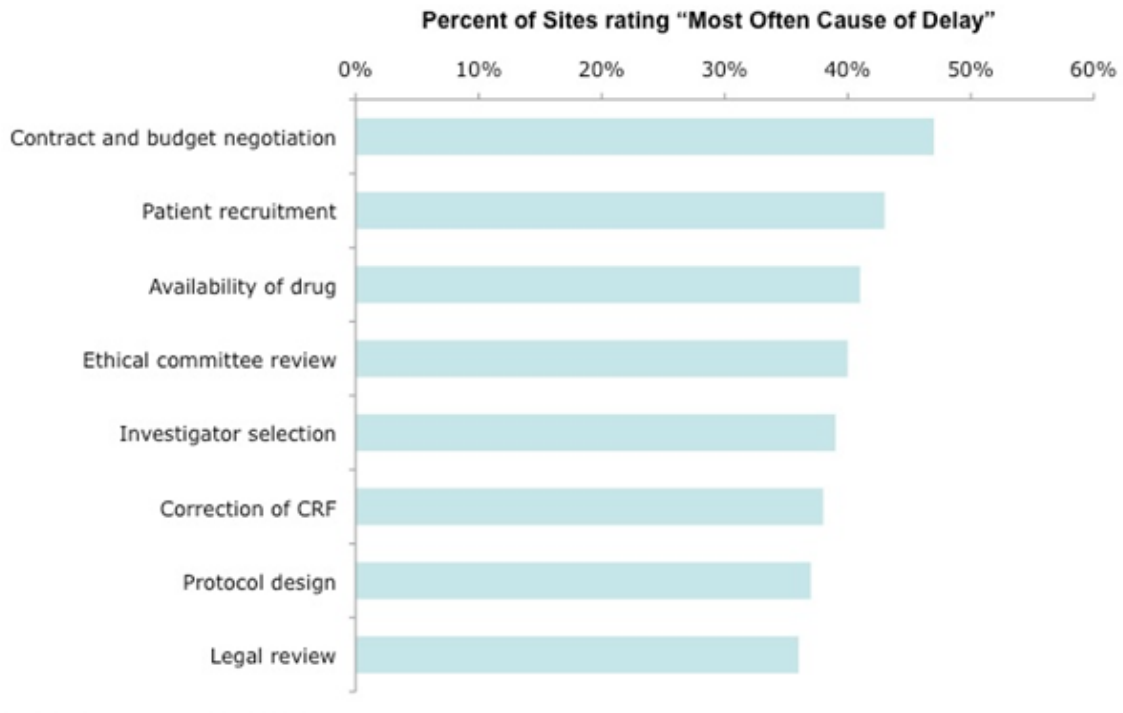

Figure 34: Causes of clinical trials delays. Representative graphic of the causes of clinical trials delays. Reproduced from source [40].

- The quality of the protocol.

Protocol design, its correct interpretation and the necessary amendments are appointed as causes for delays and have a very high impact. Pressures on R&D spending and the necessity to obtain faster results are the reasons for the growing tendency to submit protocols that aren't fully mature yet and that, consequently, require more amendments throughout the approval process. These can be visualized on Figures 25 and 27 where we observe a strong increase on the number of amendments in the last seven years (from 64 amendments in 2006 to 332 in 2012) [6]. It is very important to improve the quality of protocols to reduce amendments and the waste of time and also to allow a correct interpretation of the protocol with consequences, for example, on the improvement of recruitment.

In addition, the requests for clarification and amendments are frequently send in the end of the legal time to be approved and normally are inconsistent, systematically changing the legal deadline [8].

- Difficulties in negotiation the Financial Contract.

This document states the financial terms and other details between the sponsor and the clinical trial sites and, after a consensus is achieved by both parties, still needs to be approved by CEIC. In Portugal, the time for this negotiation is very long. This is an administrative factor that needs to be improved, in the best interest of both, the sponsors and the sites. The result will be a reduced time for initiation a clinical trial [27]. It is important to refer that there isn't a legal deadline for this approval and that is may take several months [8].

- Lack of procedures and harmonized politics related to clinical research.

Added to the long time that hospital administrations take to analyze and review the contracts (which most of the times only begins after the approval of CEIC and INFARMED) we have the lack of clear politics and harmonized procedures, resulting in an extended time for CT approval [41].

- Failure response time to the Feasibility Questionnaire.

The FQ is sent for several sites in many countries by the sponsor. These FQ will provide the sponsor the necessary elements it needs to evaluate which site or sites are best to perform his clinical trial. The timeliness of the sites' answer is very important and demonstrative of the interest and motivation to participate in that clinical trial. However, in Portugal, there are many sites that do not comply within the intended timeframe. This is very negative both for the reputation of the site as even for the Portuguese itself reputation because our

country becomes connoted to the idea of failure, not compliance and lack of interest. This negative situation is an important reason why, sometimes, the sponsors do not contact Portuguese sites for conducting clinical trials. Meeting deadlines becomes more important when sites are contacted by CROs that also have deadlines to meet with the sponsor [42].

- Unrealistic answers to Feasibility Questionnaire.

Another problem related to FQ is the common unrealistic answers provide by the sites. This occurs because sites, with the objective of attracting more clinical trials, provide unrealistic answers to FQ, namely the number of patients that can be recruited. The result is that the site is chosen by the sponsor based on the FQ answers but when the clinical trial actually begins, the site cannot meet the expectations and may jeopardize the clinical trial. This removes credibility to the centre and explains the big difference between the numbers of planned patients versus patients really included. This is also a reason for sponsors and CROs to lose confidence in Portuguese sites [42].

- Failure time to the recruitment.

The recruitment phase is the period during which sites can include patients in the clinical trial. Also because of unrealistic answers to FQ, many sites in Portugal don't have the capacity to include the planned patients during the recruitment time given by the sponsor and also take a long time to include the first patient. In Portugal, the amount of time elapsed between the proposal to perform the clinical trial, and the recruitment of the first participant, is, on average, one year. This is very disadvantageous mainly in competitive clinical trials where the period for recruitment is over as soon as the intended number of participants is achieved, independently of the sites of inclusion. One clinical trial that needs to include 100 participants within three sites: a Portuguese site, that planned to include 20 participants, a Spanish site that planned to include 30 participants and a French site that planned to include 50 participants. If it is a competitive clinical trial and, at the end of the first month of the recruitment, the French site has included 73 patients, the Spanish site has included 25 and the Portuguese site has included 2, the recruitment phase will be finished. So, the Portuguese site, that could have included 20 participants, only included 2. This example is the reality in Portugal [42].

- Lack of research sites of excellence.

Portugal has some good research centres but there is a gap related to the necessity of hospitalization and more specialized equipment, as for phase I [42]. The creation of specialized sites is very important, with a clinical trial management team, experienced physicians in clinical trials and proper standardized operating procedures [41].

- Lack of cooperation for clinical research.

In Portugal there is an inefficient share of knowledge and CT are performing autonomously by each sponsor or each researcher [8].

- Top 8 of sponsors are constituted only by international companies.

A significant slice of clinical trials performed in Portugal is sponsored by international companies. For these companies, the major reason to invest is a globally favourable environment in clinical research. If the environment isn't the best, they can easily transfer the clinical trials to other countries [8].

- There are few clinical trials performed in primary health care units.

This is a result of the law restrictions related to conditions, infrastructures and support researchers for performing a clinical trial.

It is important to implement the creation of conditions to perform clinical trials in these sites: cooperation mechanisms with sites, partnerships with community pharmacies to control the experimental drug circuit and medical emergency protocols with local hospitals [8].

- There are few investigators initiated trials.

The conditions to promote independent clinical research are limited in Portugal. There are few investigators with fund, support, partnerships and enough qualified support structures to perform a clinical trial. It is important to review the legislation, in order to facilitate the sponsorship to investigators, for example by eliminating or decreasing taxes, reducing administrative complexity and costs and supporting the submission of clinical trials. For example, in Spain the exemption of taxes for the projects performed by independent investigator has been already enacted [8].

Therefore, to solve these problems it is imperative to improve the flexibility in the negotiations between sponsors, CROs and sites. It should be certainly useful the existence of a financial contract model that could regulate the negotiations even between different sites. It is also crucial that the site has a timely and realistic answer to the FQ. The cooperation among all stakeholders is of utmost important. We have to take as example the African Proverb "If you want to go fast, go alone; if you want to go far, go together".

Human Resources

Another obstacle to the realization of clinical trials is the technical human resources available in Portugal. We have very good healthcare professionals but whose training hasn't had the

clinical research as priority. It is fundamental to reinforce the training of the healthcare professionals (introduce mandatory subjects on research during the degrees and post degrees, recognize and value the clinical research careers [41]) in order to target and differentiate human resources for research. It is also fundamental to support research teams, involve healthcare professionals in innovative projects, encourage, support and recognize the clinical research career in order to ensure that healthcare professionals consider the clinical research an important activity. Clinical research certifications can be created as well as cooperation between academic institutions, healthcare units, healthcare companies and regulatory authorities in order to improve the development of healthcare professional's competencies and recognition of their qualifications [8].

Another problem is that, for the majority of healthcare professionals, the research activity is perceived as add-on tasks, specially the assistance activity, because we have a lot of hospitals without specific human resources affected to the clinical trials [41]. This results in a lack of motivation of the professionals principally because the clinical research requires a lot of time (it is necessary to register a lot of information about the patient, the patient requires a lot of care and a lot of administrative requirements [43]) and dedication by everyone involved [42]. It is important to enable them with the possibility of choosing the area of work: clinic or research. The full-time dedication to clinical research is fundamental. With this specialization we will find more efficacy, dedication, motivation and positive results. The team responsible for conducting CT should be constituted by different types of professionals such as physicians, nurses, pharmacists and study coordinators. In order to guarantee a smooth conduction of the CT everyone's role must be well documented.

Patient Recruitment

Patient recruitment and retention is of utmost importance because it contributes to determine whether clinical studies comply with the timelines.

One cause for the poor recruitment rates in Portugal can be the lack of divulgation and information of the clinical trial to the patients. In Portugal the main stream and almost only source of recruitment is through the own medical practice of the researcher and medical references from professional colleagues [42]. However, there are many other sources that aren't used in Portugal, because of the legislation restrictions, but are used in other countries like [43]:

- Government employees (e.g. military);
- Private industry (e.g. clinics in large industries);

- Referrals from clinical laboratories;
- Mass media strategies (via newspaper or radio advertisements);
- Mass mailings;
- Community screening;
- Participants in other clinical studies;
- Blood banks (blood donors);
- Local advertisements (notices on bulletin boards);
- Site Specific Database;
- Other sources (see chapter of V).

These sources are very important for the advertising of a clinical trial and for the increase of eligible patients for the study. If Portugal wants to achieve the recruitment rate levels from other countries, will need, urgently, to develop specific legislation for advertising clinical trials. However, this is only the first step. After that it is still necessary to carry out an important amount of work through information and awareness of the patient to participate in the study. This is important because many of those who were aware of the clinical trial option refused to participate because a lot of factors such as a possible of ineffective new treatment, getting in the placebo arm and out-of-pocket expenses [10]. It is very important to change these ideas and transmit to the patient all information about the clinical trial, with an appropriate language so that he can understand, mention the potential benefits of their participation and essentially giving him confidence without pressing the patient. It is also important that the patient feels free to ask all the questions and get all the information to show to the family and friends [42]. There are several factors that influence patient recruitment and that should be taken into account to improve the recruitment, such as [43]:

- Source of patients referral: medical sources, other clinical studies, clinical laboratories, blood banks;
- Number of patients contacted via letter, telephone, or direct approach using mass mailing, mass media, friends, advertisement or other methods;
- Specific place where mass screening occurs: at workplace, educational facility, social group, community location or elsewhere;
- Socioeconomic composition of the patient pool;
- Location of the study site relative to patients' home or work;
- Degree of concern that patients have for their disease;
- Nature of patients appeal to enrol in the study;
- Specific requirements and demands of the study (in terms of difficult or disagreeable tests);

- Amount of remuneration or other benefits (meals, transportation) given to patients;
- Hire additional personnel to help recruit patients;
- Conduct additional medical chart reviews and/or reviews of pharmacy records;
- Determine what is motivating patients to enter as well as not to enter in the clinical trial and attempt to address patients needs;
- Review hospital admissions or clinic appointments to seek potential patients;
- Provide a tour of the clinic for prospective patients and answer their questions;
- Devote more time to recruitment and give it a higher priority in terms of efforts.

There are also retention strategies like [10]:

- Dialoguing assistance: intensify communication and intervention;
- Visit reminders;
- Compliance reminders: use phone and texting reminders;
- Educational support;
- Treat all participants well and give them attention;
- Ensure feedback is provided sensitively and quickly;
- Ensure any retribution or compensation are processed swiftly;
- Understand any signal of lack of interest to combat and prevent retention problems.

Another important measure to give confidence to participants is the publication of the clinical trial results. This is essential, even when the results are not expected ones. For patients, is important to know the results and understand that they are always a source of development and progress. For other researchers they are essential, at least, to know that way isn't the best way [42].

It is urgent to improve the recruitment. To help in the screening of eligible patients it should be important the bet in the development of informatics tools for hospitals to introduce all the information about all patients, which would greatly facilitate the patient research by characteristics needed for clinical trial. If Portugal is a small country with few patients, we have to make all efforts to have an efficient recruitment. To improve the advertising of clinical trials, an investment in the information and awareness of eligible patients may be the solution [42]. Why not invest in awareness by proximity and work this issue in healthcare centres and pharmacies?

We also can take the example of United Kingdom and promote initiatives that involve society like the creation of a portal "people in research" where there are news, divulgation and the integration of people and patients in groups of work related to clinical research and a bet in the specific divulgation, publication and documentation about the benefits of clinical trials. Also in this country the legal barriers of disclosure were minimized in order to

promote the recruitment. In some material of promotion of clinical trials phase I in UK it is even referred the payment to participants. This initiative is also a simplification of law and a diminution of bureaucracy [8].

In Portugal, the importance of CT divulgation was understood by CEIC. In order to clarify and adapt its position having in mind the evolution of society a document was developed with some ideas. It was under public discussion until February 2013. In this document it was highlighted the necessity of divulgation of CT because it isn't acceptable that the CT information was available only for some patients. However, CEIC clarified the difference between divulgation and advertising, refused all type of advertising and restricts the type and how information can be transmitted because CEIC didn't ignore the human-being vulnerability in case of disease. Therefore, even though the tendency is to improve the divulgation and the information about CT, Portugal is still far from having types of CT disclosure similar to other countries [33].

Other aspects

Funds and financial incentives for clinical research.

The fund provided by the State Budget for laboratories and research has declined. In 2012 it was €74.5 millions but this year it is only €65 millions [44]. The financial incentives to clinical research aren't paid on due time or even never paid to sites and researchers. This is very discouraging. The review of fiscal incentives is also important as they may be seen as an investment incentive and may improve the competitiveness of our country [8].

For example, in UK, a National Institute for Health Research was created in order to manage funds to support investment. In the period between 2012 and 2017 it approved a package of 102 million Pounds for the development of 19 Clinical Research Facilities for Experimental Medicine [8].

Policy and Strategy

In Portugal there is a lack of recognition of the strategic importance of clinical research for the improvement of health care and national economy. The result is the disinvestment and the loss of competitiveness. The nonexistence of a strategy for clinical research has resulted in maladjustment of the laws that regulate the sector, inefficiency of financing systems,

discouragement for the improvement of sites conditions and creations of research networks [8].

Hospital administrations

There is a discomfort of administrators related to clinical trials. Some of them don't recognize the importance of clinical trials for the hospitals and they have their institutions focused on clinical practice. So they are reticent about clinical trials because they think about the increase of costs with medicines, with human resources and they are unprepared to evaluate and approve a clinical trial [8].

IV.II. SWOT Analysis of Clinical Trials in Portugal

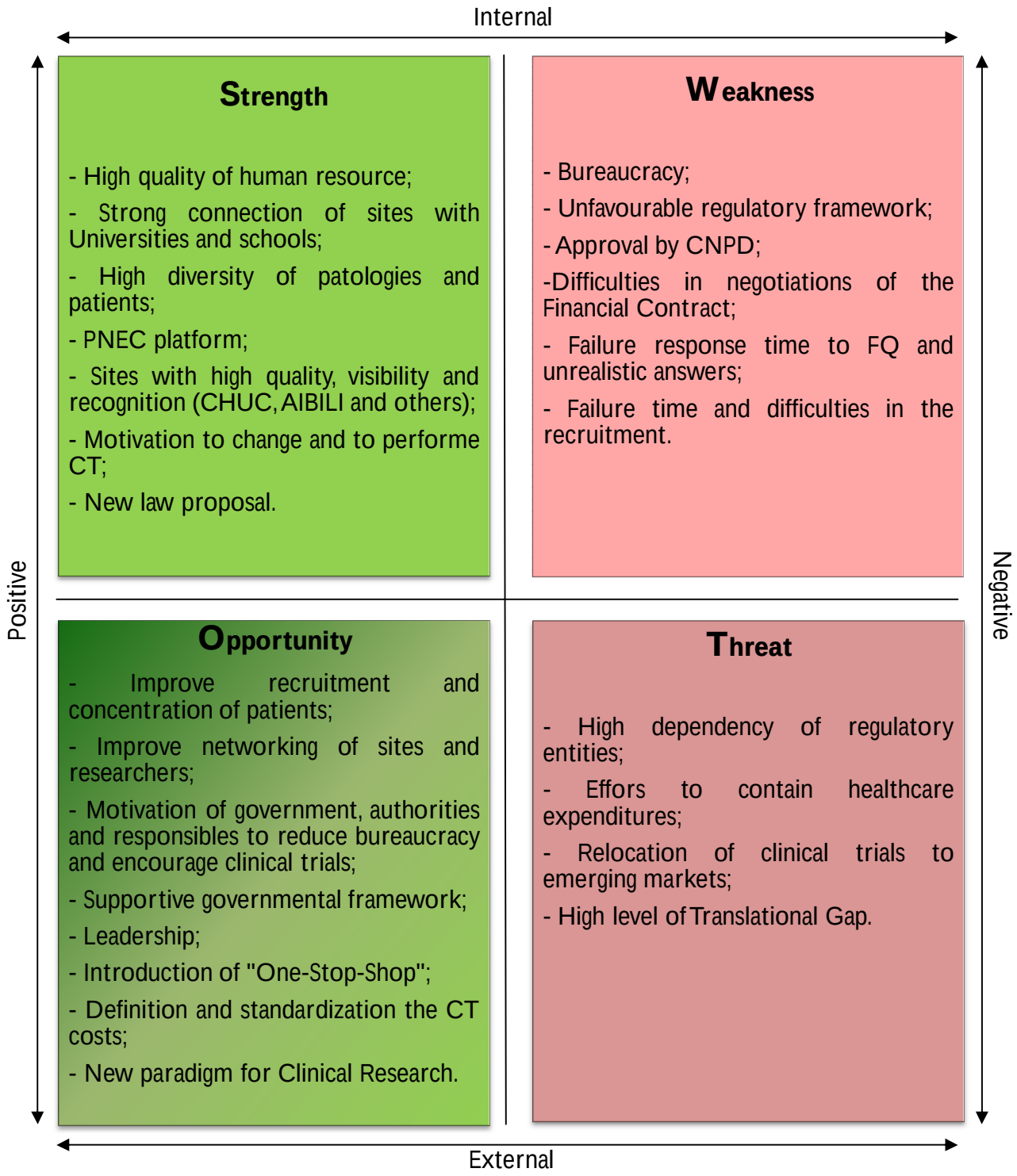

Figure 35: SWOT analysis of clinical trials in Portugal. Evaluation of Strengths, Weaknesses, Opportunities and Threats involved in clinical trials performed in Portugal. Adapted from sources [23, 26, 27, 38, 42, 44-47].

IV.III. Possible Strategic Plan to Promote Clinical Trials in Portugal

Being aware of the main issues related to clinical trials in Portugal, it is urgent to develop a strategic plan for the promotion of CT that should complement the possible solutions that have been already enumerated along the present dissertation. Success cases as Belgium, Czech Republic and Austria should be an example for Portugal that has the duty to know and implement the measures followed until now by these countries.

Figure 36: Necessary changes. Changes needed for organizations in order to allocate more clinical trials. In top 3 are standardization, networking and transparency in clinical trials costs. Adapted from source [6].

The main strategies taken by these countries were: improve the local legal framework, define clear guidelines and more transparent communications, improve access to patients and promote networks of clinical trials centres [6].

- **Networking** of specialist expertise centres and healthcare professionals.

In order to facilitate the pooling and sharing of expertise, best practices and transference of key knowledge between centres, it is also important to avoid fragmentation of competencies and improve access to patients. An independent organization dedicated exclusively to clinical research can be created. Its mission should be the development of clinical research and the articulation between all stakeholders [6].

- Evaluation of the introduction of a **"One-Stop-Shop"** principle.

To access relevant researchers and hospitals (Denmark), there is an on-line portal for submission of trial applications where both the competent authority and ethics committee approval processes are centralized. It should also standardize, centralise and harmonise processes like ethics committee and competent authorities' approvals, patient information, clinical trial contract agreements, financial negotiation formats and informed consent forms made available to applicants through the portal. The portal ought to be linked to a clinical trial register indicating which trials are recruiting as well as a patient registry that can assist in the localisation of suitable trial participants. This would lower cost and time efforts, while improving transparency and access to patients and key information [6].

- Develop a **Supportive Governmental Framework**.

The main objective is facilitates the access to innovative drugs based on standardization and centralisation [6].

- It is important to ensure the optimization of the regulatory and legal aspects.

Try to define and implement shorter deadlines for the approvals and also for the validation of the submitted documentation that shouldn't be longer than 24 hours and create guidelines to define deadlines for the approval of the financial contract are some examples [8].

- Define and standardize the CT costs in order to promote their transparency [6].
- Improve the recruitment, implementing strategies like those already listed.

Create a work group focused only on the recruitment (like in France whose objective was "recruit much, much, faster and better.") and whose key actions include promoting clinical research, harmonise procedures to shorten the set-up time of clinical trials, provide human resources to support researchers and support a national network of clinical trials, clinical trials sites, healthcare professionals and patients [6].

- Provide training and education to clinical trial centres and their staff.

It is important to share best practices, standardise trainings, develop mechanisms for accreditation and raise the level of clinical trials know-how in order to strengthen their competitive reputation of quality and expertise [6].

- Provide training and education to competent authorities and ethics committees.

The objective is ensuring training in relevant multi-disciplinary expertise in order to raise the bar in terms of approval times and their processes [6].

- Provide training and education to researchers, patient organisations and patients.

It will increase the motivation to participate in clinical research projects and in CT [6].

- Provide training and education to whole community.

It will highlight the vital importance of the CT in Portugal [6].

So, the strategic plan can be summarised into 3 key steps:

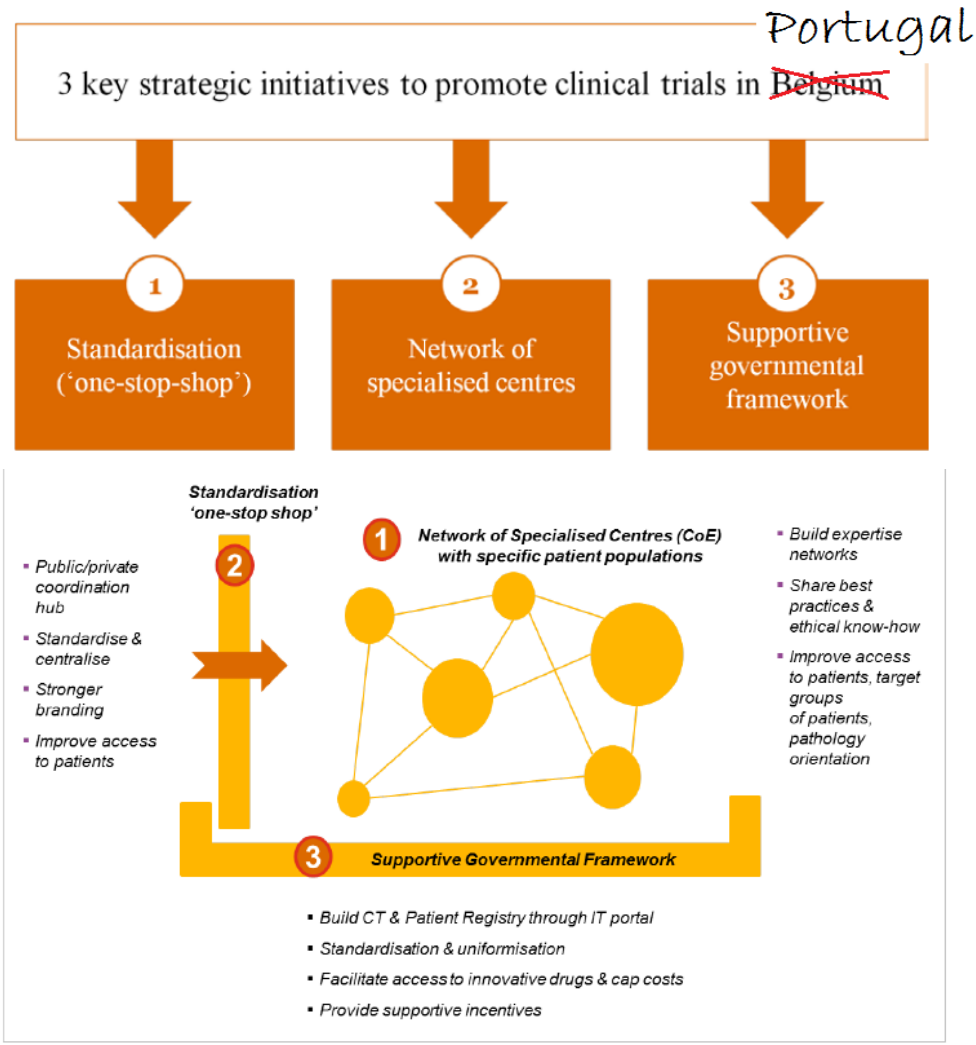

Figure 37: Strategic plan. 3 Key strategic initiatives to promote clinical trials. Adapted from source [6].

Without the implementation of any strategies or measures that could minimize the actual hurdles to clinical research and clinical trials, it is estimated that the future evolution is the same of occurred between 2009 and 2012 and will be a negative impact of 4% on the volume of clinical trials [8].

V. The Role of the Pharmacist

The pharmacist is a health professional whose intervention during a clinical trial is very important. The broad training of a pharmacist enables this professional to give an enormous contribution to clinical research and clinical trials.

The pharmacist is present since the beginning of the development of the new medicine when we have this professional in a laboratory working in R&D and applying its knowledge about chemistry and pharmacology. In the Galenical & Analytical development laboratory we can also find pharmacists doing a great job.

After that, the pharmacist is also present in the production of the experimental medicine where the objective is to make a medicine complies with every specification with high standards of quality.

Related to the performance of a clinical trial, it is possible to find pharmacists as members of INFARMED, CEIC and CECs with a relevant role in the analyses of clinical trials and with influence in their approval.

When the clinical trial is approved, we have pharmacists working in the elaboration of all clinical trial documentation and with the responsibility of organizing the Quality Management System (QMS). In all levels of organization of quality activities we can have a pharmacist even to perform the tasks of Quality Assurance Officer.

Closer to the medicine, we have the pharmacists that are responsible for the experimental medicine at sites and consequently for its storage, control and dispense. For that, the pharmacist has to establish rules and procedures whose compliance is mandatory and are the guarantee of the good management, handling, conservation and administration of the experimental medicine to the patients. Related to this task, the pharmacist has the obligation to make all recommendations related to the administration of the medicine (about doses, frequency and time) and also inform the patient about possible adverse reactions and possible interactions, with other medicines or even food and drinks [48].

However, I think that society and particularly clinical research have to take more advantage from this professional, from his/her skills and from its proximity with all population. I am talking particularly about pharmacists who work in community pharmacies. This healthcare professional is very competent and has two real characteristics that can improve the performance of clinical trials. The first is the very good distribution and proximity to the population especially to patient population (in many cases is the unique contact of healthcare professionals with some patients) and the other is that the majority of the population recognizes the competence of this professional, which is very important to transmit credible

information and to educate and enlighten the population. We have a great opportunity to use the pharmacy channel to transmit information about clinical trials and to inform people about the advantages of clinical trials for population. With this, we can organize informative campaigns about the real objectives of clinical trials and try to finish with the idea that participants are “guinea pigs”. Pharmacists can also advertise specific clinical trials and help in the recruitment, directing eligible patients for clinical trials centres.

Another participation of the pharmacist and pharmacies can be the support to the idea of the realization of more clinical trials in units of primary health care. For this to be possible, we have to guaranty that the experimental medicine is transported and available in these sites under controlled conditions and on time. With Portuguese pharmacies network and the ethical and professionalism of pharmacists, we can control the circuit of the experimental medicine [8].

In the end, we have another important contribution of the pharmacist, the collaboration in educational programs by the organization of meetings, debates, conferences an even university courses, masters and post-graduations of awareness and specialization in clinical research [48].

Final Conclusions

In 12 June 2013 a minister said that clinical research was a fundamental area for a continuous quality improvement, it was a way to have access to innovative treatments, encourage the creation of centres of excellence, improve the knowledge and project Portugal to the first line of technological development. It is a good signal when clinical research and its importance are recognized in the Portuguese Parliament and by our governments. It is a good signal when they recognize the role of authorities in providing conditions for the development of good and qualified clinical research and set priorities when these priorities serve as guidelines and haven't got a limiting role. It is a good signal when they recognize the imperative necessity of health care professional's motivation, of theirs formation and of the revision of their contracts [49]. It is a good signal so that the society can understand the importance of clinical trials [29].

As many voices said, it would be a sign of culture and modernity, if the government and hospital administrators admitted the catalytic role of clinical research and considered it as an investment. Maybe that time has come.

Some people are beginning to invest in human resources of quality, technical capacity and innovation, so clinical research and clinical trials may turn out to be one of the major competitive areas in Portugal [29].

There is still a long way to go since we have less than 10% of the potential that clinical trials can generate. However, the current situation can be a positive factor because it predisposes to change and if the interests of all stakeholders are assured, the future of clinical research in Portugal will be guaranteed [29].

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Appendix

I-Tables from Chapter III.III "Portuguese Overview".

Table 10: Number of active substances studied by chemistry and biotechnological origin (2006-2012). Adapted from source [32].

Origin of the Active substance(s) of the IMP(s) being tested	***2006***	***2007***	***2008***	***2009***	***2010***	***2011***	***2012***
Chemical origin	107	103	102	75	72	54	76
Biological / Biotechnological origin	41	29	41	34	26	26	37
Chemical & Biological / biotechnological origin	5	0	3	6	9	8	5
Total (CTA submitted and valid)	***153***	***132***	***146***	***115***	***107***	***88***	***118***
% of Biotechnological Active Substances	***30%***	***22%***	***30%***	***35%***	***33%***	***39%***	***36%***

Table 11: Number of clinical trials promoted by Pharmaceutical Industry and Academical Researchers (2006-2012). Adapted from source [32].

Status of the sponsor	***2006***	***2007***	***2008***	***2009***	***2010***	***2011***	***2012***
Pharmaceutical Industry (commercial)	145	127	139	103	101	82	112
Academical (non commercial)	8	5	7	12	6	6	6
Total (CTA submitted and valid)	***153***	***132***	***146***	***115***	***107***	***88***	***118***
% Pharmaceutical Industry	***95%***	***96%***	***95%***	***90%***	***94%***	***93%***	***95%***

Table 12: Number of substantial changes of approved clinical trials (2006-2012). Average time of decision in the same period. Adapted from source [32].

Substantial amendments notified for authorization	***2006***	***2007***	***2008***	***2009***	***2010***	***2011***	***2012***
Notifications Submitted (N)	64	97	158	244	305	327	332
Notifications Authorized (N)	52	84	155	218	259	267	282
Notifications Not Authorized (N)	NA	0	0	0	1	0	2
Average time for authorization (Days)	NA	38	25	24	20	23	23
% In time	NA	60%	97%	96%	100%	99%	99%

II-Personality interviewed

Maria Luísa Ribeiro, PhD, Director of Clinical Trials Centre (CTC) of AIBILI (Association for Innovation and Biomedical Research on Light).

III-Short Biography of the Personalities referenced in this dissertation

James Lind

James Lind (the cover photograph [50]) was born in Edinburgh in 1716. He was a Scottish physician and was a pioneer of naval hygiene. In 1731, he registered as an apprentice at the College of Surgeons in Edinburgh and in 1739 became a surgeon's mate. In 1747, while serving as surgeon on HMS Salisbury, he carried out experiments to discover the cause of scurvy, whose symptoms included loose teeth, bleeding gums and haemorrhages. So, by conducting the first ever clinical trial, he developed the theory that citrus fruit cured scurvy that allowed that scurvy disappeared almost completely from the Royal Navy [12].
After this experiment, in 1748, Lind retired from the navy and went to Edinburgh University to take professional qualifications and practiced privately as a physician. In 1753, he published 'A Treatise of the Scurvy' and in 1757 'An Essay on the Most Effectual Means of Preserving the Health of Seamen in the Royal Navy'. In 1758, he was appointed chief physician of the Royal Naval Hospital at Haslar in Gosport where he investigated the distillation of fresh water from salt water for supply to ships. In 1763, Lind published work on typhus fever in ships and in the 1768 publication 'An Essay on Diseases Incidental to Europeans in Hot Climates' he summarised the prevalent diseases in each colony and gave advice on avoiding tropical infections. Lind died in 1794 in Gosport [12].

Maria Luísa Ribeiro

With a Medical Doctor degree in Ophtalmology and a Master in Ophthalmology by University of Coimbra is the director of the Clinical Trial Centre (CTC) of AIBILI since 1994 and the main researcher since 2003 until present, in the same institution. Until that was Ophthalmologist resident in the Dept of Ophthalmology at University Hospital of Coimbra in which Luísa Ribeiro has the position of sub-investigator since 1996 [51].

Her clinical and research experience gives her the possibility of coordinating and performing a lot of clinical trials with fairly good results and with a fantastic recruitment rate which reveals an efficient work and which brings recognize and prestige for the CTC of AIBILI [51]. Her love for the research and sharing of scientific knowledge have made that, since the beginning of her career, she has been participated and contribute for a large number of publication and communications in various areas like diabetic retinopathy and macular edema and even performed some courses like "Introductory course to Clinical Research" [51].

Luís Almeida

"CEO at Luzitin SA (www.luzitin.pt), Managing Partner at Blueclinical Ltd (www.blueclinical.com) and Managing Partner at ARC Publishing (www.arc-publishing.org). Director of the PharmaTrain-affiliated Masters and Post-Graduate Courses on Pharmaceutical Medicine (pharmaceutical-medicine.pt), and Vice-Director of the Doctoral Programme on Health Sciences and Technologies, University of Aveiro, Portugal. Specialist in Clinical Pharmacology and Pharmaceutical Medicine, Luis Almeida has over 20 years of experience in drug development.

With a Medical Doctor degree and a PhD degree in Medicine by the University of Porto, Luis Almeida was the Director of the Medical and Regulatory Affairs Department of Zyma Farmacêutica Portuguesa (CIBA Group) between January 1990 and April 1996. Then, he joined BIAL (Portela & Co SA), as Head of Clinical Research and Deputy R&D Director. During his 13-year career at BIAL he was responsible for setting up a phase I unit for studies in healthy volunteers and for defining and supervising the clinical development programmes of BIAL's new chemical entities. Over 100 clinical trials were conducted under his responsibility.

Luis Almeida is inventor/co-inventor of 6 international patents, and author/co-author of over 65 papers in peer-reviewed journals, 125 abstracts/proceedings, 2 book chapters, and over 200 posters/oral communications at scientific meetings.

Specialties: Pharmaceutical medicine, clinical pharmacology, clinical research, drug development, electronic health records, photodynamic therapy, personalized medicine.

He has been playing different jobs and functions:

- Managing Partner- Blueclinical Ltd: Drug R&D consultancy, phase 1 clinical trials (including bioavailability/bioequivalence) and clinical research management;
- Managing Partner-ARC Publishing: Statistics and scientific writing services. Scientific publishing;

- CEO- Luzitin, S.A.: Member of the Management Team of Luzitin SA, with the role of Chief Executive Officer (CEO). Luzitin's Mission is to investigate and develop innovative compounds to be used in Photodynamic Therapy (PDT) or Photodynamic Diagnosis (PDD) of cancer and other diseases, thus contributing to the human wellness;
- Director, Masters and Post-Graduate Course on Pharmaceutical Medicine-Health Sciences Department, University of Aveiro, Portugal**:** Management of a Training Programme on Pharmaceutical Medicine at the University of Aveiro. The programme is recommended by the AMPIF (Portuguese Association of Pharmaceutical Medicine Physicians) and affiliated at the IMI PharmaTrain. The Training Programme is organized in modules aligned with the PharmaTrain's European Training Syllabus for Pharmaceutical Medicine. The teaching staff is composed by experts from the Portuguese and foreign universities, regulatory authorities, pharmaceutical, biotechnology and medical devices industries, and contract research organisations (CROs);
- Head of Clinical Research and R&D Deputy Director-BIAL (Portela & Co, SA)**:** Responsible for the clinical development programme of 6 new drugs, including eslicarbazepine acetate, nebicapone, etamicastat, trans-resveratrol and opicapone;
- Director, Medical and Regulatory Affairs Department-Zyma Farmacêutica Portuguesa Lda (CIBA Group): Deputy Managing Director; member of the Executive Committee and Marketing Committee; management of medical affairs, regulatory affairs and clinical development;
- Medical Advisor-CIBA Vision;
- Medical Advisor-Zyma Farmacêutica Portuguesa, Ltd;
- General Medical Internship-Hospital S. Joao".

In linkedin- http://www.linkdin.com/in/jluisalmeida at 01/07/2013 [52].

IV-Quality Management in Clinical Research

All clinical research related activities are performed under a Quality Management System. The sponsor is ultimately responsible for the quality and the integrity of the trial data but all sites should have their own system for quality control and quality assurance [53].
The QMS aims to document and standardize, by means of written Standard Operating Procedures (SOP), all the critical clinical research activities, in order to maximize the

efficiency of the processes and to assure full compliance with good clinical practices and the legal and ethical requirements [45].

There are important documents like Trial Master File (TMF) that is kept by the sponsor and has relevant information about clinical trials. The investigator must keep the Investigator Site File (ISF) of essential documents that allows the inspectors to access how the trial was done and the quality of data and show whether the trial followed the relevant EU directives. These documents should be generated and on file before the trial starts and any new information must add to the files during the trial to show that is documented as it becomes available [53].

The documentation is very important and all documents have to be written, authorized and should [53]:

- Be complete, legible, genuine, traceable to a specific trial and readily available;
- Not be altered without permission and creation of an audit trail;
- Keep a current version at each point of use;
- Remove obsolete versions from circulation, but keep copies for reference;
- Review the procedures regularly;
- Inform staff of any change or any new ones;
- Keep records that make it possible to trace which version of a SOP was current at any given time;
- Not be copied without control, without the registry of the number and location of each copy and without the guarantee that the copy is certified for accuracy, completeness, isn't lost or changed;
- Be restrictive access, only to authorized people.

A specific person should be responsible for the documentation and their storage in order to guaranty all previous parameters and the correct storage (in adequately facilities and during the regulated time) [53].

Proper QMS implies consequent implementation of the Quality Assurance, through planned and systematic action, to provide adequate confidence that the clinical trial and the documentation will satisfy given quality requirements. These actions should be checked by someone independent of work (the Quality Assurance Officer) [54].

A major part of the quality assurance is the Quality Control that is "the operational techniques and activities that are used to satisfy quality requirements" [54].

All these three levels of organization of quality activities are very important to production quality and to guaranty that the clinical trial and its results are complies with the requirements and that its data are reliable.

AIBILI

Association for Innovation and Biomedical Research on Light and Image is a Research Technology Organization (RTO) in the health area dedicated to the development and testing of new products for diagnostic imaging and medical therapy [51].

AIBILI is the Coordinating Centre of the European Vision Institute Clinical Research Network – EVICR.net that is a network of European Ophthalmological Clinical Research Sites, dedicated to perform clinical research in ophthalmology with the highest standards of quality, following the European and International Directives for Clinical Research according to harmonized SOPs. At present, EVICR.net has 76 Clinical Site Members from 16 European Countries [51].

AIBILI has been recognized in 2010 as a Champalimaud Translational Centre for Eye Research by the Champalimaud Foundation (C-TRACER) for its activities in translational eye research. The Champalimaud Foundation has been progressively establishing a network of C-TRACERs involving major eye research centres looking for collaboration in a global perspective. This network is of major relevance to AIBILI because it brings together under the Champalimaud Foundation three major eye research institutions in the World and creates links between three major continents, Asia, Europe and South America [51].

AIBILI is organized in Research Centres and Supporting Units where highlight Coimbra Coordinating Centre for Clinical Research (4C) and CTC.

The 4C is a qualified structure to support Researcher-Driven and Industry-Sponsored clinical trials activities according to ICH GCP and the EU Clinical Trials Directives. 4C permanent staff includes five study managers, one statistician, one informatics specialist and one administrative secretary [8].

CTC has dedicated facilities and the most modern ophthalmological equipment. Permanent staff includes three medical doctors, one pharmacist, three technicians for diagnostic procedures, six study coordinators and two administrative secretaries. 20 other medical doctors, three technicians for diagnostic procedures and four nurses collaborate regularly in the CTC activities [8].

The professional organization of the CTC and its convenient location, next to the University Hospital of Coimbra and the Celas Unit Health Administration of the Central Region of Portugal, are a guarantee of efficient recruitment and that the deadlines are successfully met

and in compliance with the ICH Good Clinical Practice Guidelines. As we can analyze in the graphic below, AIBLI has an efficient recruitment.

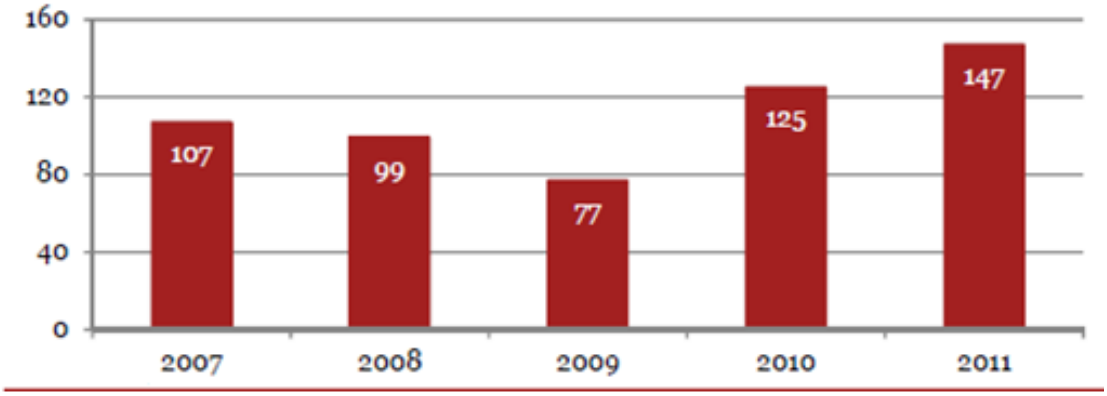

Figure 38: Recruitment rate (2007-2011). Recruitment rate in clinical trials is very high (% of planned). In 2011 147% of the planed patients were included. Reproduced from source [8].

The CTC is certified by ISO 9001 to perform clinical trials, thus guaranteeing the continual improvement ICH-GCP compliance. CTC is also certified as Clinical Site of Excellence by the European Vision Institute Clinical Research Network (Clinical Site nº 1), that is a clinical trial centre in ophthalmology that complies with ICH GCP Guidelines with written SOPs, has the necessary equipment and personnel to perform clinical trials and has proven expertise and scientific publications in this area.

The number of ongoing clinical trials has been increased. During 2012 it had 11 researcher-sponsored clinical trials ongoing and 17 industry-sponsored clinical trials [51].

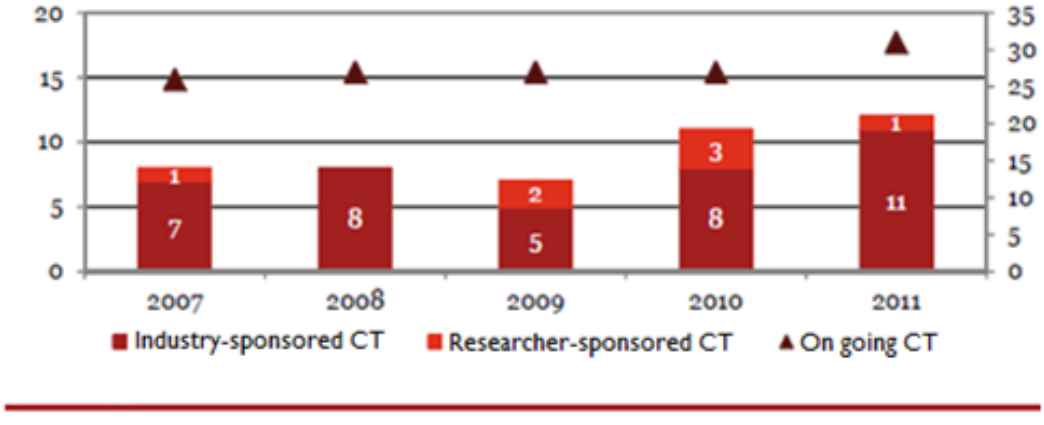

Figure 39: Initiated and ongoing clinical trials (2007-2011). The number of ongoing clinical trials has been increased. Adapted from source [8].

The main factors for the success are establishing an organization dedicated to clinical research consisting by a qualified team, with vanguard equipment and fulfilling the legal and

quality requirements and also the integration of international research networks and the international recognized resulting of the publications.

As a result, AIBILI has great operational results:

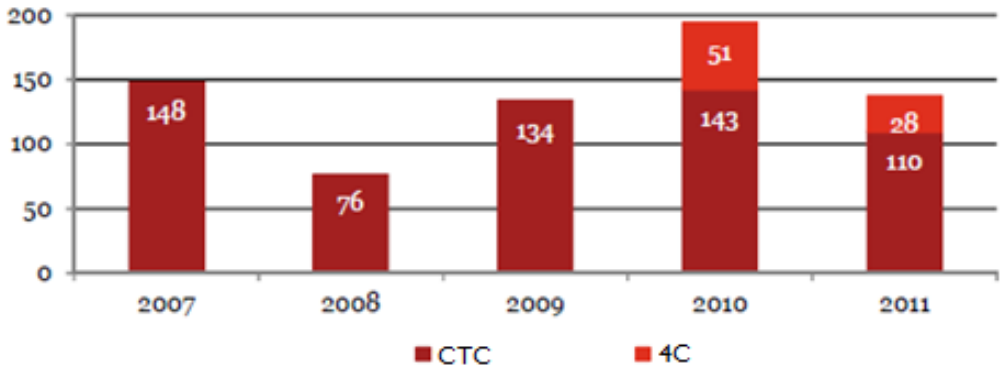

Figure 40: Operational results (2007-2011). Operational results are the result of the difference between operating income and costs (thousands of €). Adapted from source [8].

This represents also a great advantage to the National Health System that can save much money. For example, a clinical trial related to age macular degeneration, that has treated and followed 12 patients, will save €100000 to the budget of Health National System [8].

Blueclinical

Blueclinical is a recent player. Its action plan can be divided into three main activities focused on clinical research:

- R&D consultancy: it provides expert advice and supporting institutions and businesses in the development of their projects with a view to the marketing [45]:
  - Analysis of business plans, preparation and implementation of pharmaceutical, preclinical, clinical and regulatory development plans of new drugs, medical devices and other health products;
  - Preparation and monitoring of scientific and regulatory advice with INFARMED and foreign regulatory authorities;
  - Planning and supervision of pharmaceutical development and analytical methods;
  - Definition and supervision of the implementation of the nonclinical development plan;

- Preparation of the investigator's brochure and the investigational medicinal product dossier;
- Definition and supervision of the clinical development plan;
- Ethics approval and regulatory approval for clinical studies;
- Portfolio selection support;
- Support in the preparation of the business plan and application for funding.

Its mission is developing activities of "Translational Medicine" in Portugal, through support for institutions and companies (especially start-ups) in their I&D projects [29].

- Clinical Research Site Management Organization: the objective is to ensure successful research in the research centres supported by Blueclinical, promoting their growth, efficiency gain and achieving a reputation for excellence in clinical research through the creation of highly motivated and organized research teams, who are focused on complying with all applicable legal requirements and the best ethical and quality standards. With this help, the institutions can improve their structural and administrative organization, which is the major limitation to the efficiency of clinical research [45].
- Blueclinical Phase I: clinical research unit of human pharmacology located at Hospital da Prelada, Oporto. It focuses on the conduction of phase I studies and early proof-of-concepts studies in healthy subjects and in selected patient populations. Its experienced staff performs studies like tolerability and pharmacokinetics, drug interactions, food effect and bioavailability/ bioequivalence studies [45]. The unit has 650 m^2 and it has a team of 26 people (including 7 doctors and 10 nurses) [29].

The creation of this company was born of one gap in clinical research in Portugal, related to phase I clinical trials and the research in healthy subjects. The lack of centres of excellence to perform clinical trials and theirs organizational deficit was also in the origin of Blueclinical.
Its staff is highly experienced in drug R&D planning (preparing and submitting the documentation of studies to the authorities) and in conducting clinical trials of any phase. Its technical and scientific skills are unique in the Portuguese landscape and these places Blueclinical on the front line of clinical research in Portugal [45].
With the networking of knowledge which is being constructed by Blueclinical, this company will be briefly recognized as a partner to take into account at the international level, for an excellence clinical research [29].

CHUC

The University Hospital Centre of Coimbra was created in March 2011 with the fusion of the University Hospital of Coimbra, Hospital Centre of Coimbra and Psiquiatric Hospital Centre of Coimbra in a total of eight hospitals (two general hospitals, two maternities, three psychiatric hospitals and one paediatric hospital) [55]. In total, it has 7800 employees, 1976 beds and it represents 10% of hospital expenditure in the country and 10% of the GNP of "Baixo Mondego" [46].

Concerning clinical trials, CHUC has extraordinary conditions to perform clinical trials. It has all medical facilities and a high number of patients, which translates annually in 66500 hospitalizations, 50000 surgeries and 880000 external consultations. During the period between 2006 and 2011 CHUC was in the first place in the ranking of the number of clinical trials per site in Portugal, with an average of 158 clinical trials. In 2012 they performed 176 clinical trials, a third of the total performed in Portugal. The objective is to allow access of their patients to innovative medicines and treatments in an earlier phase and also the possibility of placing these treatments, medicines, diagnostics methods and also medical devices on the market. CHUC has also a great recruitment rate in clinical trials. For some of MCT performed, CHUC was the site that recruited more patients and, in other clinical trials, CHUC was the site that included the first patient for a clinical trial [46].

For that, Coimbra Research was created to help the affirmation of Coimbra as the Portuguese Health Capital and with the support and work of various institutions and companies of the region (Biocant, Instituto Pedro Nunes, Critical Health, MedicineOne and Bluepharma) [46].

Furthermore, CHUC will receive the first centre of clinical trials of phase I in Portugal. This centre is a big bet on the clinical trials and in innovation. With that, Portugal, Coimbra, researchers and patients will be facing the most recent innovations. This project will be working in spaces that were unoccupied, after the CHUC reorganization, so the investment will be small. It has tremendous advantages like the development of phase I clinical trials in Portugal, the access to new medicines in early phases, the creation of employees and also the improvement of international visibility. This centre will complete the supply of CHUC that has been performed clinical trials of phase II, III and IV. This centre has also the objective of consolidating the leading position in areas such as neurology, neuroscience and cardiology [44].

CHUC will also create a Centre of Integrated Responsibility dedicated to clinical research in order to achieve more autonomy and flexibility to adapt the technical and human resources to the necessities [44].

Eurotrials

Eurotrials is a CRO founded in Lisbon in 1995. It specialises in clinical research and scientific consultancy in the health area. It has several areas of activity including R&D and CT. With R&D activity, Eurotrials has the aim of improving health research while establishing a link with the market. It has all the competences and experience needed to operate in the drug development, analysing projects and drafting plans for strategic and regulatory development. Related to CT, they develop and monitor CT in Europe and Latin America [56].

Eurotrials has also an independent department of quality with vast experience in quality control and quality assurance, including GCP audits. In addition to outsourcing, they ensure that all work of the Eurotrials departments complies with ISO 9001:2008, the legislation in different countries, the rules of good clinical practice (ICH-GCP and GCP Directive) and any other applicable regulations [56].

After 18 years, Eurotrials is a partner of reference for clinical research and scientific consultancy in health area in Portuguese-speaking countries. The company's success stands on: creativity in finding solutions, unique technology, multidisciplinary expertise, solid experience and quality. It is qualified to participate in all the steps of any clinical, translational or epidemiological research project, from the initial research question to the final output [56].

Eurotrials counts with a diversified and interdisciplinary team in order to meet its customers' needs. It is a link between pharmaceutical industry, sites and hospitals, universities, CROs, foundations and institutions, financial groups, consultancy firms, health regulatory authorities, health professionals and patient associations [56].

Eurotrials has also an important role of sharing experience and knowledge. It has been developing training programs and activities that are tailored to meet the needs of different groups, in close collaboration with the pharmaceutical industry, medical societies and clinical research departments. More than 2200 health professionals have participated in 1520 hours of activities. In CT area we can emphasize the course of monitor of CT whose mains are: to recognize the importance of CT, to understand the cycle of clinical research and CT, to understand all process of regulatory submission, to meet national and international laws and regulations and to meet the stakeholder of CT and their responsibilities [56].

Portuguese Clinical Research Infrastructure Network

PtCRIN's Portuguese Clinical Research Infrastructure Network is a national research infrastructure hosted by Nova Medical School and Portuguese Society of Pharmacology. The aim is to facilitate and improve quality in clinical research and encourage national and international research collaboration for the benefit of patients, citizens and the healthcare system. PtCRIN will strengthen and link several existing centres and will actively promote collaboration between them [57]. It will be the hub to support multi centre studies and to attract to Portugal international academic clinical trials managed by ECRIN (Europe Clinical Research Infrastructure Network), whose aim is to support multinational research by promoting a network dedicated to improving the health of patients through clinical research. ECRIN synergizes the capacities and capabilities of national research and harmonize European clinical research [58].

PtCRIN focuses on academic clinical trials because they provide answers to crucial clinical questions, they are at the practical end of translational research, they promote an environment of know-how and trial efficiency (which in turns attracts the industry trials) and they are a sector that needs support. Taking advantage of ECRIN support, the objective is improving the number of academic CTs led by Portuguese investigators that, at the moment, is negligent (2-4/year). The aim is to develop and organize specific infrastructures to provide services and support the investigator to implement CT and comply with ICH-GCP guidelines, European CT Directive and national legislation. These services will be available to the clinicians willing to undertake academic clinical trials [57].

With the PtCRIN integration in ECRIN, Portugal has already obtained some funds which can capacitate Portuguese clinical research. PtCRIN will be able to bring additional funds from the EU, international health industry and other sponsors [57].

There is already a network of institutions and hospitals and also a formation program to improve the competencies of investigators, nurses, study coordinators and other health professionals, and to guarantee their continuing education.

New law proposal

In May 2013 a new law proposal, related to clinical research, was approved in the council of ministers, without any votes against. The main goal is the transversal application of the ethical evaluation through the regulation of the approval and performance of clinical trials

process. The appreciation regime of CEIC becomes generalized as well as the establishment of sponsors, researchers and sites liability [47].

The same proposal also provides the creation of a National Registry of Clinical Trials. The objective is to improve the authorization process and the transmission of all relevant information. On the other hand it will improve the access to information about which clinical trials are performed in Portugal for general society and health professionals [47].

The most relevant aspects are [49]:

- Clinical research regulation since the evaluation of the performed processes, advertise and sharing of resources;
- Introduction of a glossary of clinical trials that is fundamental for necessary regulatory framework;
- Streamline approval processes of clinical trials;
- Clarify the role of CEIC and CECs creating a networking of ethical Commissions, standardizing procedures and sharing specialized resources, consultancy and reciprocal recognition of opinions;
- Horizontal application of ethical evaluation by the generalization of evaluation and approval processes;
- Strengthen the role of the CEIC;
- Create obligations for responsible advertising of clinical trials with a correct identification, interpretation and control;
- Protect voluntary participants;
- Creation of a National Registry of Clinical Trials and the obligation of registration of all stakeholders in order to obtain a complete platform of all clinical trials and the improvement of stakeholders interaction and the development of quality clinical research.

This is the beginning of the recognition of the importance of clinical research by the government and political leaders. This can mean the beginning of clinical research recognition as relevant strategy for Portugal improvement. This can be the beginning of the necessary supportive governmental framework and it is good news for clinical research.

PNEC

National Platform for Clinical Trials is a portal with relevant information related to clinical trials. In this portal we can find information about laws, the procedures to perform a clinical trial and statistics about Portuguese clinical trials. The portal is also an open platform where

the interaction between the different partners of clinical research (CROs, regulatory authorities, sponsors, researchers, sites and patients) is promoted [25].

The main objectives are identifying the problems for the performance of clinical trials in Portugal, promoting clinical research, increasing the number of clinical trials and developing centres of excellence to perform clinical trials in Portugal. The final objective is encouraging the development of high quality research for the benefit of patients [25].

This portal also gives us information about the activities organized by PNEC, INFARMED, CEIC and other related organizations. It is a connection point between these organizations and their websites [25].

With the objective of promoting clinical trials and clinical research, this site also has information about possible formations that improve the competences and *Curriculum Vitae* of the health professions that have interest in this area [25].

PNEC also allows the electronic submission of amendments in the marketing authorization. With this platform, Portugal was one of the first countries with the option to submit amendments notifications via internet. Companies can also follow the status of their requests by using this platform [25].

But the goal of PNEC is to go further and facilitate the submission of new clinical trials and projects, through electronic submission of the documentation. The implementation project of this portal is still ongoing and is important its promotion through of [8]:

- Centralization of all electronic submission process “one-stop-shop”;
- Promotion of information about ongoing clinical trials and recruiting clinical trials in order to facilitate the recruitment;
- Certification of sites and researchers;
- Promotion of data about the activity of sites and researchers in order to promote the performance and competitiveness in Portugal.