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Economic Efficiency of Countries' Clinical Review Processes and Competitiveness on the Market of Human Experimentation

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ABSTRACT

Clinical research is a specific phase of pharmaceutical industry's production process in which companies test candidate drugs on patients to collect clinical evidence about safety and effectiveness. Information is essential to obtain manufacturing authorization from the national drug agency and, in this way, make profits on the market. Considering this activity, however, the public stakeholder has to face a conflict of interests. On the one side, there is society's necessity to make advances in medicine and, of course, to promote pharmaceutical companies' investments in this specific phase (new generation). On the other side, there is the duty to protect patients involved in these experimental treatments (old generation). To abide by this moral duty, a protection system was developed through the years, based on two legal institutions: informed consent and institutional review board. How should an efficient protection system that would

take human experimentation into account be shaped? Would it be possible for the national protection system of patients' rights to affect the choice of whether to develop a clinical trial in a given country or not? Looking at Europe and considering a protection system that is shaped around institutional review boards, this article is an empirical work that tries to give answers to these open questions. It shows how a protection system that can minimize the time necessary to start a trial can positively affect pharmaceutical clinical research, that is, the choice of pharmaceutical companies to start innovative medical treatments in a given country.

Keywords: clinical research, efficiency, pharmaceuticals, protection system of patients' rights.

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Introduction and Theoretical Background

According to international guidelines and declarations, such as the International Conference on Harmonization of Good Clinical Practice—which provides a unified standard for the European Union (EU), Japan, and the United States, as well as those of Australia, Canada, the Nordic countries, and the World Health Organization—the Helsinki Declaration [1], or the Nuremberg Code [2], the protection of human rights for subjects in clinical trials has to be assured. Each country receives these international documents with its own national rules, even if with different final implementations. However, a common rule that goes beyond national identities is that each clinical trial has to be authorized by an ethics committee before patients are involved. This ethics committee, also called institutional review board (IRB), is an independent committee designated to approve and monitor clinical trials involving patients, with the aim of protecting the rights and welfare of these subjects against the necessities of the community. Obviously, the IRB is not a unique legal institution behind the protection system of patients' rights. Another relevant institution is the informed consent, which is the legal key through which the patients acquire information and express their will. This institution deals with important biomedical ethics issues regarding therapeutic misconception, which is

the patients' inability to understand that they are being used for clinical research, receiving innovative medical treatment with uncertain effectiveness.

The main patients' right concerns their freedom of choice. Indeed, the idea of research subjects' rights grew at the end of World War II when Nazi experiments on Jews and prisoners were discovered. From that terrible experience, society felt that it had the duty to prevent research involving people as subjects for experiments not of their own free will. Currently, patients have to be informed about the experiment (i.e., expected effectiveness, as well as all expected/unexpected adverse events) and they cannot be involved without their consensus. This is the main patients' right in the domain of human experimentation that is assured by the informed consent.

Taking the last 50 years into account, there are more examples of the necessity to protect patients, that is, more examples of abuses from the strongest parties (i.e., pharmaceutical companies and/or physicians) versus the weakest (i.e., patients). As mentioned above, the idea itself of ex-ante control to check the scientific validity of the clinical protocol, as well as the freedom of choice, is strictly linked to World War II and Nazi experiments. There are other more recent instances, however, such as the *Vipeholm experiment* (Sweden in the fifties) where, to learn more about dental health, the effect of carbohydrates on dental caries

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Published by Elsevier Inc.

<http://dx.doi.org/10.1016/j.jval.2012.09.010>

was tested on patients with mental illnesses [3], or the *Willowbrook experiments* (the United States in the sixties) where researchers gave live hepatitis viruses to children with mental retardation to study the disease and ultimately develop a vaccine for it [4].

Up to now, the main problem with a protection system shaped around review boards concerns the conflicts of interest that affect members of these IRBs, as Barnes et al. [5], Barnes [6], and Goldner [7] state. Other interesting currents of thought concern IRB's decision-making methodology, that is, the effectiveness of its practices. Indeed, according to Coleman [8], there is a great deal of evidence that IRBs are "... often incapable of reviewing complex research protocols effectively ...". To increase the current bibliography, this article tries to analyze the protection system of patients' rights from another perspective: efficiency, that is, the boards' ability to minimize the required time to review a clinical trial.

Society is made up of healthy and sick people and, obviously, there is the necessity to guarantee both health and economic development. Indeed, even if there are some risks, (i.e., expected and unexpected adverse events), clinical trials can represent a useful and free path to upgrade physicians' knowledge and thus the health care system they work for. At the same time, experimental medical treatment is free. This means public saving and therefore lower taxation, at least in those countries with a strong public welfare system (e.g., European countries), as well as higher access to innovative medical treatments (both in the United States and in Europe). The proposal of free experimental drugs where there is not a strong public welfare system (i.e., the United States) has been studied deeply as undue influence, as well as the proposal of paying research subjects [9–11]. Moreover, taking medical centers into account, there is evidence of the positive impact of clinical research on their reputation [12]. Finally, another opportunity for healthy people could be satellite economic activities.

This means that the public stakeholder would face a trade-off that could turn into a hornet's nest. Considering innovation in medical knowledge, Calabresi [13] argues that it is necessary to have "... an adequate balancing of present against future lives and still sufficiently indirect and self-enforcing as to avoid clear and purposive choices to kill individuals for the collective good ...". This is the trade-off that a policymaker has to face in building an appropriate protection system. In other words, the public stakeholder has to consider that increasing the degree of the protection system of patients' rights, that is, the rules adopted to guarantee respect for patients, could lead to pharmaceutical disinvestment in that country.

According to Ippoliti [14], in a global competitive market of human experimentation, the protection system of patients' rights could cause a shift in the supply of health care innovation toward another country. The author suggests the existence of a specific submarket within the market of medical care proposed by Arrow [15], in which innovation is exchanged for information, where the former is given by experimental medical treatments (i.e., the difference, in terms of expected effectiveness, between the experimental treatment and the current one), whereas the latter is given by clinical evidence about experimental treatments (i.e., evidence about the safety and effectiveness of candidate drugs). According to this idea of market, the national protection system of patients' rights and its ex-ante authorization process can affect the above-mentioned exchange, as well as the competitiveness of countries. This competitiveness is based on transaction costs, that is, the costs necessary to obtain ethical opinions on an experimental protocol and to start the exchange. In other words, the lower the time (or the required conditions) necessary to perform the exchange of innovation for information, the higher the number of experimental activities implemented by

pharmaceutical companies and, therefore, the higher the national competitiveness on the market of human experimentation. Obviously, focusing on the time necessary to start a clinical trial, this work only considers IRBs' activity and what can affect their efficiency. Note that a competitive system does not imply the effectiveness of this system in the protection of patients' rights. Indeed, a long process of revision made by the IRB could be more effective in the protection of patients' rights, even if it is less competitive in the market of human experimentation. This work focuses only on the efficiency of the protection system and how it could affect countries' competitiveness.

This is the specific background in which the proposed analysis is shaped. Companies develop new molecules inside their laboratories and then they proceed with the patent process. The life of a patent is 20 years, and before authorization to manufacture is obtained, evidence concerning this new product is necessary. Obviously, the shorter the testing phase, the higher the expected profit. In other words, the efficiency of a protection system could affect the time required to test the innovative drug and thus increase the future expected profit.

Current bibliography can support the appropriateness of the proposed approach, considering both the issue is related to the regulation and the one is linked to the outsourcing of medical research.

Adobor [16] suggests how "... pharmaceutical companies benefit from cost-savings and reduced time in getting their drugs to market ..." as well as "... global pharmaceutical giants such as Novartis, Astra Zeneca, Eli Lilly, and Pfizer continue to outsource medical research globally ...". Among several keys, the author recognizes regulation as a potential explanatory variable of pharmaceutical companies' localization of the testing phase, especially considering the need for speed in drug development. Indeed, as suggested by Bodenheimer [17], each day's delay in gaining Food and Drug Administration approval of a drug, the manufacturer loses, on average, \$1.3 million in potential revenue. Moreover, studying the Food and Drug Administration, Gauch [18] also suggests that "... approval delays also cost the drug sponsor because they are not able to start receiving a return on their sizable investment in developing a drug ..." as well as "... statistics had shown that drugs were being approved sooner in other countries and that made the FDA appeared overly cautious ..." Obviously, as has been aforementioned, the main consequence of this issue is the outsourcing of clinical trials where there are better conditions, that is, where the regulation might be more competitive and/or more relaxed (i.e., emerging markets). According to Adobor [16], multinational corporations such as Pfizer, Eli Lilly, GlaxoSmithKline, Sanofi Aventis, and Roche have started clinical studies abroad, with India the preferred destination. Other leading emerging destinations include Indonesia, Thailand, Mexico, Brazil, and South Africa [19], with China angling for a piece of the outsourcing pie [20]. Evidence of relaxed regulation has been collected in these emerging markets: clinical researchers have tested illegal drugs and conducted studies without IRB approval [21], as well as there is no IRB at all and when present, there may be conflict of interest between members of the IRB and medical researchers/pharmaceutical companies [22].

Considering regulation, the main related concept in the proposed background is the transaction costs, which has been introduced by Coase [23] studying market organization and firms. The assumption of positive transaction costs, instead of zero costs, has begun to take hold only after two decades, as well suggested by Coase himself [24]. This turning point is due to two contributions [25,26] in which authors underline the necessity to study the real world of positive transaction costs and the failure of many current theories. In the following years, the idea of positive transaction costs was deeply analyzed, especially in

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