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An Empirical Analysis on the European Market of Human Experimentation

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Abstract

The target of this work is to support the thesis that pharmaceutical companies' testing phase would be treated like any other form of production in a globalization process, that is to say, a specific phase of pharmaceutical R&D could be localized where the cost of clinical evidence is lower.
Considering Europe, an empirical analysis in order to support the main hypothesis is performed. Taking trials of phases II and III, funded by Industry (dependent variable) and the main macroeconomic features (independent variables) of each nation into account, the empirical work is implemented via regression analysis on panel data (2000 - 2007). The sample analyzed considers EU-27 plus the candidate states (Croatia, the Former Yugoslav Republic of Macedonia, Turkey), Norway, Switzerland and Iceland.
Results suggest the appropriateness of this process since clinical research is clearly affected by economic conditions, regardless of the scientific purpose.

Introduction

When appraising national health care systems, one of the main characteristics that is taken into account concerns patients' access. Obviously, the ageing process can only make this issue even more pertinent in political debates, and thus health care for everyone is among the most important aims of policymakers.
In any social state there is the necessity, on one side to guarantee health care for all sick people, but on the other there are constraints linked to the national budget, as well as interest in not laying all the burden on future generations. Several solutions have been adopted by administrations, such as using generic drugs or making patients more responsible. Although measures differ from country to country, all of Europe agrees that something has to be done to make health care less costly, especially after the financial crisis of last year. An important component of the industry of health care goods and services is the pharmaceutical one. In detail, we can expect two different supplies of medical

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treatments through drugs: the well-known supply of settled medical treatments and the experimental one. Both are offered to patients by pharmaceutical companies on the health care market.

In order to establish both the safety and effectiveness of new drugs before their manufacture is authorized, an experimental phase is required by regulatory agencies. This could be an opportunity for all potential research subjects to receive care using the latest and most innovative medical treatment. In this way pharmaceutical companies would invest in drug testing helping the national health care system to save money. In addition, the experiments would help the physicians involved to keep up to date with the latest advances in the cure of different pathologies. If this approach were adopted, patients would be viewed as a national resource instead of a delicate problem to be faced by society. This could mean that countries would compete with each other to implement clinical trials funded by pharmaceutical companies.

Physicians are involved in this activity as medical researchers whereas patients as research subjects. The key of this research activity is the physician-patient relationship as well as the informed consent session. Indeed, after a discussion with the medical researcher, all research subjects have to sign the informed consent to be enrolled in the trial (Faden et al. 1986; Braddock et al. 1997). However, there are still some open issues regarding therapeutic misconception (Appelbaum 2002; Appelbaum et al. 1982, 1987; Daugherty 1999; Emanuel 1995; Freedman 1990; Miller 2000), that is to say, the patients' inability to understand the activity in which they are involved. An interesting work on patients' misconceptions of therapies has been carried out by Sankar (2004)[2]. The author suggests the idea of a framing strategy adopted by physicians in the informed consent process behind therapeutic misconception. The proposed approach is compatible with many researches on decision making process (Ariely 2008; Blumenthal 2004; Jolls et al. 1998) as well with the *prospect theory* suggested by Kahneman and Tversky (1979).

Moreover, in the field of ethics undue influence on patients involved in experimental treatment has been discussed extensively, especially, taking economic incentive into account, by Grady (2001), Ripley (2006) and Dickert et al. (2002). However, taking economic interest and undue influence into account, only the patients' side has been deeply analyzed up to now. This paper tries to consider the issue from another prospective, that is to say, assuming economic influence on the medical researcher, how this potential undue influence can affect national clinical research.

Starting from their analysis and recalling the idea of Arrow (1963)[3] with regard to the *medical-care market*, Ippoliti (2010) suggests the existence of a specific *sub-market* in which the interactions among pharmaceutical companies and patients can lead to an exchange of clinical evidence with innovation in medical treatment. According to the proposed idea, countries could compete by providing an efficient rule system that would guarantee the safety of all patients involved in the trials as research subjects, but minimizing the transaction costs linked to the testing phase. A protection system of patients' rights should be shaped around the Institutional Review Boards (IRB), as well suggested by Calabresi (1969).[4] However, considering the failure of that ideal market, an interesting development could concern countries' competitiveness with regard to the new (and real) price of clinical evidence. In other words, assuming an

[2] The author defines frame as "…the background expectations that we bring to an interaction, or that motivate an account or a narrative…". Moreover, she suggests "…framing is the way we impose those expectations or promote one account over others. At its simplest level, framing uses inclusion and exclusion to juxtapose and arrange elements in order to signal or impose a particular account or frame…". Framing strategy and patients' delegation process will be combined together in this paper, in order to suggest the physician's behaviour in the enrolment process of research subjects.

[3] Arrow (1963) suggests that a market exists which is characterized by risk and uncertainty in medical treatments supplied by the medical-care industry, as well as a demand for services in which sick people are affected by a mechanism of trust and confidence in the choice of a physician. The decision making process of patients, used in this work, is shaped around the delegation process between physician and patient, as well as his idea of a medical-care market.

economic interest behind medical researchers (fee), an interesting development could concern the study of how countries competitiveness on this imperfect market could be affected by physicians' behavior. According to this idea of market failure, countries could compete depending on medical researchers' attitude towards making a profit, that is to say, there could be an opportunity to set up an appropriate system of incentives in order to minimize the expected cost of pharmaceutical companies to collect evidence on candidate drugs.

This paper is mainly an empirical work whose aim is to study the European market of clinical research thereby showing that it actually exists, analyzing the impact of economic variables on countries' competitiveness (i.e. physicians' fee) and offering an explanation of pharmaceutical companies' strategies in the last few years. The sample analyzed considers EU-27 plus the candidate states (Croatia, the Former Yugoslav Republic of Macedonia, Turkey), Norway, Switzerland and Iceland.

In the first section all potential data are presented, that is to say, all data that could represent the realm of human experimentation are introduced. Finally, in the second section, taking trials of phases II and III, funded by Industry (dependent variable) and the main macroeconomic features (independent variables) of each nation into account, the empirical work is implemented via regression analysis on panel data (2000 - 2007).

The conclusions regard the policy maker's point of view, that is to say, how national competitiveness could be increased on the European market of human experimentation, as well as presenting an agenda of future developments.

Methods

The dependent variable of this analysis is represented by clinical trials of phases II and III, funded exclusively by the pharmaceutical industry.[5] All types of studies have been included in the data-set, i.e. studies with pharmaceuticals, vaccines, devices and procedures. The data used are studies that started in Europe from 2000 to 2007, and were collected by the U.S. National Institute of Health (NIH).[6] In this work Europe is considered as a group made up of 33 countries: EU-27 plus candidate states (Croatia, the Former Yugoslav Republic of Macedonia, Turkey), Norway, Switzerland and Iceland. These countries will be the sample of observations used in the statistical analysis.[7]

[4] Considering generational conflict behind human experimentation, Calabresi (1969) argues that *Review Board* is an expression of the value of research that involves human subjects, suggesting that it is the best legal tool through which society can protect patients' rights. Starting from his considerations, this paper will consider the protection system as having a key role in the proposed market (i.e. its regulation).

[5] Studies of phases I and IV are not considered, since the first involve healthy people whereas the second, regardless of the fact that it involves patients, is affected by marketing processes. Moreover, studies funded by universities and public agencies are not considered since the aim of this paper is to study the economic interests of medical researchers and how this could affect national clinical research.

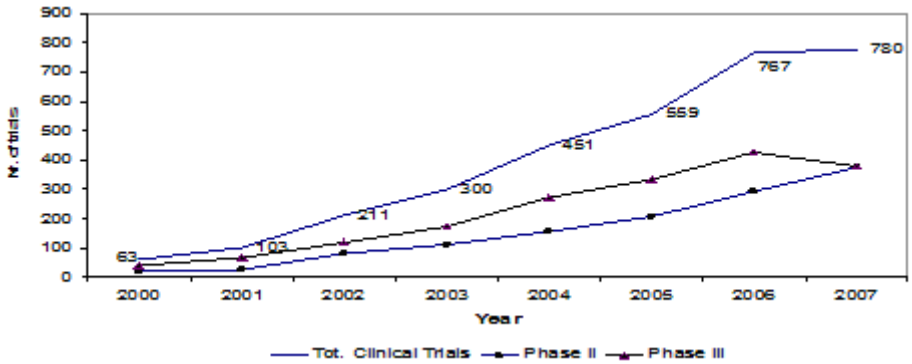
[6] Data has been extracted from the on line database of the U.S. National Institute of Health: www.clinicaltrial.gov (June 2010).

[7] This choice is affected by data availability as well as the necessity to respect the condition of minimum technology. In other words, without specific data, it could conceivably be true that in the considered sample all European countries have medical centers with those technologies necessary to do a trial, e.g. medical laboratories, something that might not be true if the sample were expanded, i.e. taking African countries into account. Note that it is assumed that satisfying a condition of minimum technology is necessary since the maximum one could be imported. For instance, if some specialist exams are necessary (e.g. genetics or bio-molecular), the sample of blood could be easily localized where the technology is (i.e. pharmaceutical companies' laboratories).

In the considered time, the total number of clinical trials set up in Europe was 3,234 with a positive trend as shown by Figure 1. Between 2006 and 2007, however, there is evidence of a setback with studies of phase III characterized by a reduction of 12%.

Figure 1:

Temporal distribution of clinical trials in Europe from 2000 to 2007



This setback occurred only in some countries. According to collected data, countries such as France, Austria, Belgium or Denmark experienced a growth in clinical research of between 40% and 70% in 2006 whereas a decrease of up to 25% in 2007. On the other hand, countries such as Hungary, Sweden, Poland or Romania were able to maintain the same level of clinical studies as before.

A consideration about the sample is necessary. This work is considering studies registered by pharmaceutical companies in an American database to study a European reality. Only studies funded by Industry have been used, and since their interest is that of obtaining manufacture authorization from FDA, the registration of clinical research on the NIH database should not be biased (i.e. studies may not have been registered). However, this is a subset of the real population and the statistical assumption is that the data is representative of the real trend in the localization process of studies in Europe. In other words, this work is assuming that the sample of pharmaceutical companies extracted from the NIH database analyzed in this paper, is representative of the whole population of pharmaceutical companies that work in Europe. This statistical assumption, supported by statistical test, gives the possibility to work on this data-set and obtain some interesting results to support the proposed thesis.

The analysis is implemented with two different approaches: the total number of clinical trials set up (both in a continuous form and in a count one) and the weight of each country in those trials. The former considers each national clinical study as a medical opportunity whereas the latter, through an appropriate index, could be considered as an economic proxy of the pharmaceutical investment in that country.

In order to give an idea of the above mentioned index, a specific year is taken into account. A total of 780 studies were implemented by 260 pharmaceutical companies in 33 European countries in 2007. Of these clinical trials, 67% were conducted in Europe whereas the remainder was done outside of Europe. In other words, 67% of the total locations activated within those 780 studies were in Europe. In this paper it will be considered as a single economic flow by the pharmaceutical industry but, within each country, this is weighted by the number of locations that are involved in the national studies. With regard to national clinical trials, that is to say, the number of studies developed in the whole of

Europe (33 countries), the number grew from 780 to 3,537. The idea of weight is closely linked to these national clinical trials and European locations.[8]

Taking *n* countries into account (a subgroup of the potential *G* candidate countries), each *i-th* country's research index is equal to the sum of clinical trials in the considered country (K_d, where d=1,…,m and m represents the total number of studies implemented in the analyzed sample), weighted to the relative frequency of country locations (*L*):

$$RESEARCH_{INDEX_i} = \left[\sum_{d=1}^{m} K_d^i \frac{\sum_{d=1}^{m} \left(L_i / \sum_{g=1}^{G} L_g \right)_d}{\sum_{d=1}^{m} \left(\sum_{i=1}^{n} L_i / \sum_{g=1}^{G} L_g \right)_d} \right] \quad (1)$$

where $K = \{0;1\}$, with 1 if activated.[9]

From these considerations, this index can represent the pharmaceutical investments in Europe. This means that a policymaker interested in pharmaceutical research both in terms of quantity (locations) and quality (number of clinical trials), should consider this kind of index in his strategy as this paper has done.

What can affect the pharmaceutical industry's choice to develop a study in a country? Considering the data available, independent variables should be able to answer this question. The strategy adopted in order to collect evidence of the existence of this market is to treat the pharmaceutical industry and its testing process like any other company in a productive process, that is to say, patients as its raw material and physicians as potential workers.[10] In other words, the experimental activity is considered like any other productive process that could be localized where the cost of clinical evidence is lower, and thus where competitiveness is higher.

We should imagine two main categories: one to approach potential research subjects and one to involve them. Of course, the former is represented by those proxies that can affect the choice of involving a physician in the trial as medical researcher, whereas the latter by what can influence the patients' choice to accept the experimental treatment.

When we consider research subjects, a relevant variable could be the Gross Enrollment Ratio (GER) that represents the "specific level of education, regardless of age, expressed as a percentage of the eligible official school-age population corresponding to the same level of education in a given school year"[11]. Recalling current bibliography, patients delegate their choice to be involved in a trial to physicians. Could GER affect this delegation process? In other words, is it possible that a high level of education can affect the patients' consciousness of the potential risks of experimental treatment and thus reduce the probability of enrolling research subjects? Or, is it possible that such a level can help patients to believe in the expected effectiveness?

On one side, the hypothesis is that in order to really understand informed consent, thought of as the legal key through which patients acquire information and express their will, an adequate level of education is necessary, more than the

[8] An example of the relationship between national locations and national clinical studies could be the following. The study number NCT00878046 was developed in Australia, Germany, France, Italy and United Kingdom (5 national clinical trials). The study had planned to involve 4 European locations of the 7 in order to enroll 100 patients (1 location for each European country).

[9] Recalling the example of note 3, we have 4 national clinical studies with a weight equal to 0.142857. Note that this work assumes that the total sample of patients is equally shared among locations. Obviously, this assumption is affected by data availability.

[10] Behind this approach, there are these assumptions: row material cost (patients) is equal to zero whereas labor (physicians) is the main one. Moreover, without loss of generalization, these workers are all assumed to be people potentially affected by economic interests. This means that the only difference in this common medical society is the cost of these workers, depending on national wealth.

[11] UNESCO Institute for statistics: http://www.uis.unesco.org, data extracted June 2010.

simple ability to read and sign a document.[12] In other words, without the ability to understand the connected risks, the patient tacitly agrees, as suggested in the previous section, and he is delegating that decision to someone else.

In other cases, if the language used in this informed consent is technical, even a degree wouldn't help the patient to understand what the physician is proposing, that is to say, just as a physician might be unable to understand the technical language used by an economist, also the opposite could be true. This means that a higher GER can't lead to lower delegation and a lower probability of enrolling research subjects.[13] Instead, it is possible that patients with a high level of education could be attracted by the description of an innovative therapy, expressed in highly technical language that is impossible for someone outside the medical field to understand. Obviously, they would also trust that the treatment would work. In order to illustrate this idea more clearly imagine what it would be like to propose a medical breakthrough to an aborigine and to a westerner. Who would believe the breakthrough might be successful? The opposite is also true. Imagine a wizard proposing a magic potion. Who would be more likely to trust the wizard? The difference between these two people is their culture and the knowledge that has been handed down to them, a knowledge that can affect both their willingness to be involved and the drug's effect on them, that is to say, the placebo effect as well as *nocebo reaction*.

The statistical analysis of the next section will help to interpret GER and thus answer this question. The data considered comes from the UNESCO database and concerns *Secondary* and *Upper secondary* level.

There is no doubt that pharmaceutical companies are interested in achieving the success that is expected from the trial. This means that a potential research subject will be selected so this goal can be most easily achieved. In other words the exclusion and inclusion criteria of a trial can be such that ideal patients are selected in order to obtain the desired result. Of course, the higher the degree of initial conditions, the more patients from a certain country will be necessary to increase the probability to enroll the wished sample. The population extracted from the database of the International Monetary Fund[14] will be considered as an explanatory variable, as well as an analytical weight to estimate countries' initial condition.

There is also another factor that can affect the choice of where to hold a trial: the physicians' fee, that is to say the main expected cost.

Let us imagine a pharmaceutical company that wishes to develop a trial. Its strategy could be to compare the cost of involving physicians as medical researchers and then to develop the trial in the most competitive country. Another variable could be patients' wealth. In other words, if there is no information on physicians' fee, it would be reasonable to assume that this fee is proportional to people's wealth since it could constitute an alternative income from the income obtained from the pharmaceutical company (i.e. opportunity cost). This paper considers the second explanation as a proxy of the physicians' fee since it is very difficult to collect this data.

A candidate variable to represent people's wealth is the gross domestic product (GDP) based on purchasing-power-parity (PPP) per capita, which also comes from the IMF database. Nevertheless some assumptions have to be made in order to use this proxy in an appropriate way. In other words, how could this proxy be interpreted using panel data?

One interpretation could be the following. If we are dealing with a global market in which there are many workers available, it would be rational for a company to choose the country in which physicians cost less. Without loss of

[12] See also Faden et al. (1986).

[13] The probability concerns patients' perception of risk. In other words, assuming people are risk adverse, in order to involve them as patients in a trial, higher effectiveness is necessary or a higher probability of achieving that wished output than a neutral one. If education implies awareness of risks, both delegation and probability to enroll should decrease.

[14] International Monetary Fund, World Economic Outlook Database, April 2010.

generalization, the main cost could be thought of as their salary. This is what has been happening in Eastern Europe over the last few years. Through the globalization of markets, factories have been transferred and employment has been growing quickly.

This suggests that pharmaceutical companies can discriminate the fee necessary to enroll the medical researcher, just like in any other productive process. In other words, assuming that the cost of the patient (i.e. raw material) is equal to zero, the cost of the physician (i.e. labor) can affect the choice of the localization of that productive process (i.e. the testing phase of a candidate drug). According to the proposed thesis, this approach is the same as in a car factory or any other productive process of goods. In this case, the good is the clinical evidence. In other words, the pharmaceutical industry and its testing phases are no different from other industrial processes. They pay fees to physicians in order to collect information about their innovative products and, of course, the lower the fees, the higher the expected profit.

Taking our panel data into account, a shortcut to demonstrate what this strategy consists of when applied to the pharmaceutical industry could be the study of how wealth that is growing quickly can affect clinical research. In other words, assuming companies are conditioned by this difference in wealth and their strategy is aimed at minimizing labor costs, pharmaceutical companies would select countries that are growing quickly (if other conditions were the same). Of course precise data is necessary, but, this could really be a credible shortcut adopted by some companies when they do not have specific information.

If the data is normalized, the index could be expressed in relation to the *n* European countries (33) average set to equal 100, that is to say:

$$WEALTH\_INDEX_i^t = \left[\frac{W_i^t}{\sum_{i=1}^{n} W_i^t / n} \right] \qquad (2)$$

where *W* is the gross domestic product (GDP) based on purchasing-power-parity (PPP) per capita of the *i-th* country in the year *t*. In this way we can measure how fast people's wealth increases in each country in comparison to the average of those countries.[15]

The hypothesis behind the companies' strategy can be supported by correlations and statistical descriptions. Taking a population of 2000 as the analytic weight and considering 180 observations[16], the correlation between the *Employment rate* and the above mentioned *WEALTH_INDEX* is equal to 0.7864 with an associate *p*-value equal to 0.000. At the same time, as shown in Figure 2, the *Average gross annual earnings in industry and services* and the indexes' variation between one year and another is equal to – 0.7081 with, again, a *p*-value equal to 0.000 on a sample of 116 observations.[17]

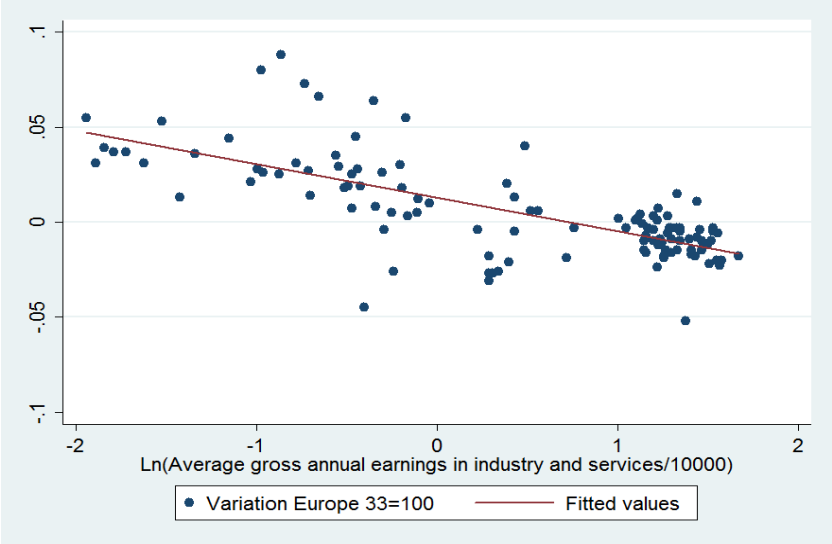
[15] Note that the index considers the trend with respect to the sample average (i.e. 33 European countries). For example, even if the German GDP on PPP is higher than the Polish one, the trend of Germany's Index between 2000 and 2007 is negative (i.e. -12.243) whereas the trend of Poland's Index is positive (i.e. + 5.187). This means that, with respect to the European average, Polish growth has been higher than average.

[16] Countries with a a population of between 700 thousand and 45 million people are considered.

[17] Sources of data: Eurostat (*Employment rate* and *Average earnings*) and IMF (*GDP on PPP*) – June 2010.

Figure 2:

Relation between national economic growth and people's earnings



This result can support the hypothesis that behind the growth of wealth there is employment (factories transfers) as a consequence of lower wealth (wages). If this is true, the GDP on PPP could be an efficient proxy to show if pharmaceutical companies are affected by physicians' fees or not. In other words, is the pharmaceutical companies' testing phase affected by (expected) lower physicians' fee?

Another interesting factor should be the number of physicians, that is to say a factor that could affect the probability of finding a potential medical researcher. The data considered comes from the World Health Organization (WHO) database, European office, and concerns the number of physicians working in health services (public or private) per 100,000 inhabitants.

Finally, in order to establish economic conditions, dichotomous variables are assumed: the adoption of the Euro and entry into the European Union. Eight countries of central and eastern Europe — the Czech Republic, Estonia, Latvia, Lithuania, Hungary, Poland, Slovenia and Slovakia — joined the EU in 2004. Cyprus and Malta also became members, but the central and eastern European countries are particularly interesting for our analysis since their economic condition could affect the choice of the pharmaceutical companies to develop a trial.[18] Is it possible that this political background could influence the strategy of the pharmaceutical companies in the testing phase?

On the other hand, 16 Member States of the European Union currently use the euro as their currency.[19] Is this common and strong currency able to affect the choice of whether to develop clinical research? In other words, is an optimum currency area able to affect the national economy as well as a specific sector, such as clinical research?

In table 1 descriptive statistics of selected variables are shown.

[18] Two more countries from Eastern Europe (Bulgaria and Romania) joined the EU in 2007 bringing the number of member states to 27 countries.

[19] The Euro was introduced in 11 countries (joined by Greece in 2001) for commercial and financial transactions only in 1999. Notes and coins came later, in 2002. The analysis takes into account the year in which the euro entered circulation (2002).

Table 1: descriptive statistics of dependent and explanatory variables.

Variable	Obs	Mean	Std. Dev.	Min	Max
Research Index Ψ	247	-1.354789	3.315419	-12.70102	4.50951
Clinical Studies Ψ (continuous variable)	264	3.134035	1.554772	0	5.993961
Clinical Studies (count variable)	264	55.85227	71.9909	0	400
European Union	264	0.6136364	0.4878404	0	1
Euro	264	0.2765152	0.4481241	0	1
Population Ψ	264	2.061927	1.342313	-0.474406	4.417348
Wealth Index Ψ	264	4.475068	0.530136	3.327	5.624
GDP on PPP Ψ	264	9.959121	0.546904	8.702	11.31
Physicians	238	313.6091	70.21549	126.25	534.59
Gross Enrolment Ratio *Secondary level*	260	102.2121	13.69727	70.49104	160.3465
Gross Enrolment Ratio *Upper than secondary level*	260	101.0416	20.84084	56.28728	194.919

(Ψ if a neper log-transformation has been applied)

Both for the *Research index* and the *Clinical studies* (i.e. dependent variables), as well as *GDP on PPP* and *Wealth index* (i.e. independent variables), a neper log-transformation has been applied in order to have a normal distribution. Moreover, a neper log-transformation has also been applied for *Population* but with the addition of a plus value before the transformation (i.e. ln[population+0.3392543]) in order to have the best possible normal distribution.
In the next sections models that have been worked out and results that have been obtained will be presented.

Results

This panel data, which is strongly balanced, is analyzed with STATA both through a multiple regression methodology and a Poisson regression model. In both cases, the dependent variable is the number of clinical trials but, in the first model it is considered continuous whereas, in the second methodology, it is a count variable.
According to Hilbe (2011), "…Random-effects estimators are more efficient than fixed-effects estimators when the data come from within a larger population of observations, as well as when there are more panels in the data…", as well as "…data coming from a smaller complete data set, with relatively few panels, prefer the fixed-effects estimator…". For these reasons, in order to reflect countries' heterogeneity, the fixed-effects option (within regression estimator) could be more appropriate since the sample of observations could not considered a random extraction from a population but

specific subjects (i.e. European countries) with particular features, i.e. the sample could represent the whole population for those given characteristics. In other words, taking potential health status of research subjects into account, as well as the welfare system of these countries, the realistic hypothesis is that the European society is considered as a whole, i.e. our sample. Moreover, to test the hypothesis of non-correlation between individual effects and dependent variables, Hausman's specification test has been done.[20]

However, in order to support the proposed thesis and to avoid a problem of collinearity, which could be linked to the fixed-effects option, the random-effects option will also be adopted. In this second case, it will be assumed that the considered sample is a random extraction of a hypothetical potential population. This approach has been applied to all models, that is to say, both to the multiple regression model and to the Poisson regression model.

Taking countries' economic competitiveness into account (i.e. proxy of the physicians' competitiveness on the market), there will be two different approaches to respect these two hypotheses of heterogeneity. On the one hand, with the fixed-effects option the Wealth Index will be considered whereas, the GDP on PPP will be considered with the random-effects option. In the first case, the analysis will try to estimate the effect of countries' competitiveness with respect to the average of the whole population (that is known). In the second case, the pure value of countries' wealth is considered since it is a random extraction from an unknown population.

Obviously, both dependent and independent variables have been plotted in order to justify the normality assumption with acceptable results, along with the residuals of each analysis. Moreover, taking the national population of the year 2000 into account, analytical weights are applied with the fixed-effects option in order to reflect the importance of the observation. Finally, in each model column A considers the Gross Enrollment Ratio for secondary level whereas column B considers for upper than secondary level.

The next two tables try to support the proposed thesis using a multiple regression model (cross-sectional time-series). The analysis will be implemented both with fixed-effects option (by using the within regression estimator in the second table) and with the random-effects option (by using the GLS estimator in the third table). Moreover, the bootstrap option with 200 replacements has been applied both to table 2 and to table 3.

Table 2: Multiple regression model (cross-sectional time-series)
Random-effects option with bootstrap
Europe from 2000 to 2007

VARIABLES	(A) Clinical Studies *(continuous variable)*	(B) Clinical Studies *(continuous variable)*	(A) Research Index	(B) Research Index
European Union	0.437***	0.420***	0.345	0.316
	(0.147)	(0.156)	(0.264)	(0.239)
Euro	0.748***	0.760***	0.400**	0.410**
	(0.129)	(0.128)	(0.186)	(0.189)
Population	0.795***	0.790***	2.213***	2.217***
	(0.0744)	(0.0844)	(0.164)	(0.136)
GDP on PPP	1.915***	1.936***	3.190***	3.319***
	(0.340)	(0.373)	(0.609)	(0.569)
Physicians	0.00642***	0.00626***	0.0109***	0.0107***

[20] Regardless of the fact that the sample without weight has been applied, the test shows, with 6 degrees of freedom and a chi-squared test equal to 70.37 (Clinical Studies) and 27.81 (Research Index), that difference in coefficients is not systematic and the null hypothesis can be rejected (p-value >chi2 = 0.0000) and that the fixed effect estimator is appropriate. See Green (2003).

	(0.00156)	(0.00165)	(0.00260)	(0.00223)
Gross Enrolment Ratio *(secondary level)*	-0.0172***		-0.00970	
	(0.00383)		(0.00736)	
Gross Enrolment Ratio *(> secondary level)*		-0.0115***		-0.00803*
		(0.00262)		(0.00458)
Constant	-18.41***	-19.15***	-40.92***	-42.29***
	(3.243)	(3.419)	(5.656)	(5.503)
F statistic (p value>chi2)				
Wald chi2(6)	559.64	587.92	425.95	423.65
Prob > chi2	0.0000	0.0000	0.0000	0.0000
R-squared				
Within	0.7425	0.7451	0.5817	0.5841
Between	0.4944	0.4892	0.6794	0.6709
Overall	0.5213	0.5210	0.6874	0.6841
Observations	218	218	218	218
Number of countries	33	33	33	33

Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Table 3: Multiple regression model (cross-sectional time-series)
Fixed-effects option with bootstrap
Europe from 2000 to 2007

VARIABLES	(A) Clinical Studies *(continuous variable)*	(B) Clinical Studies *(continuous variable)*	(A) Research Index	(B) Research Index
European Union	0.853***	0.865***	0.729**	0.743**
	(0.228)	(0.245)	(0.317)	(0.327)
Euro	1.099***	1.097***	1.044***	1.042***
	(0.168)	(0.182)	(0.238)	(0.251)
Population	12.65***	12.86***	12.16	12.39
	(4.719)	(4.904)	(8.482)	(8.284)
Wealth Index	5.370***	5.137***	8.425***	8.170***
	(1.192)	(1.254)	(1.938)	(1.938)
Physicians	0.0153***	0.0150***	0.0191***	0.0188***
	(0.00418)	(0.00468)	(0.00622)	(0.00572)
Gross Enrolment Ratio *(secondary level)*	-0.0148***		-0.0161*	
	(0.00544)		(0.00901)	
Gross Enrolment Ratio *(> secondary level)*		-0.00996***		-0.0107*
		(0.00381)		(0.00556)
Constant	-53.02***	-52.86***	-71.05***	-70.87***
	(12.24)	(12.72)	(23.25)	(22.65)
F statistic (p value>chi2)				
Wald chi2(6)	295.70	301.13	180.09	128.34
Prob > chi2	0.0000	0.0000	0.0000	0.0000
R-squared				
Within	0.6232	0.6245	0.4574	0.4581
Between	0.7456	0.7437	0.7757	0.7767
Overall	0.4696	0.4673	0.6800	0.6789
Observations	218	218	218	218
Number of countries	33	33	33	33

Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

The statistic tests (if all the regression coefficients in the fitted model are zero) are both jointly zero and thus the hypothesis is rejected. In other words the F test shows that the associated *p*-values are both equal to zero and thus the models are statistically significant. Moreover, the squares of the multiple correlation coefficients (R-sq) are good. Taking the *between* into account, the first model shows that 49% of the variance of the clinical studies is accounted for by the six explanatory variables of interest whereas, taking the number of clinical trials into account, the variance explained by the model increases to 68%. At the same time, the second model explains more than 70% of the variance for both dependent variables. Obviously, taking *pairwise* correlation coefficients between the explanatory variables into account, acceptable values with high significance level have been obtained.

With the exception of the Research Index in the random-effects option, both regressions show how the entry in the EU and the adoption of the Euro has had a positive effect on clinical research for that country. In other words, the financial, economic and political background is an attractive factor for the pharmaceutical industry. Moreover, having proven to be normally distributed, two-sample t tests with equal variances have been applied to both variables in order to verify if the two groups' observations are independent and sampled by two populations. Taking Clinical Studies into account, the difference in means is equal to -1.056 for Euro and -1.384 for European Union, with both associated p-values equal to zero.

The education effect (GER) is also interesting as far as potential research subjects are concerned in that it had been supposed in the previous section that it could cause problems for medical researchers in the enrollment process (i.e. full knowledge of risk). Taking clinical studies into account, all coefficients are negative and statistically significant, even if the goodness of the estimation decreases considering the Research Index. Moreover, the same number of potential medical researchers affects (positively) the pharmaceutical choice of developing an experimental trial in that country. In this case we have a good result for all considered analyses.

Nevertheless, the most interesting result is the proxy of the countries' competitiveness on the physicians' fee. Even if the proxy changes (i.e. GDP on PPP for random-effects and Wealth Index for fixed-effects), the results suggest the same interpretation. Indeed, in both analyses the coefficient interpretation is exactly what was expected: the growth of people's wealth (both in comparison to the average and not) is a strong factor in pharmaceutical companies' choices. Moreover, another interesting result is the effect of people's wealth and its difference in comparison to the two dependent variables. According to our interpretation, it represents a proxy of the countries' competitiveness on the physicians' fee that is higher if we weigh the number of clinical trials for the locations involved (e.g. 8.425 vs. 5.370, case A of fixed-effects option). In other words, all conditions being equal, the number of locations (number of patients involved) will increase where there are better economic conditions (profit maximization). Instead, the simple number of clinical trials (national medical options) could be more reasonably affected by the probability to enroll the desired patient. For this reason the variable concerning population growth is significant and relatively high in table 3, both A and B. In other words, the higher the population growth, the higher the number of clinical studies, but not necessarily, the number of locations involved. However, a different result can be obtained if the heterogeneity of countries is not considered.

The population of 2000 has been considered as analytical weight in the next table. Obviously, this option can be applied only to the fixed effect option, and in addition the bootstrap cannot be applied. Both presented models are statistically significant (F test hypothesis satisfied) and the variance explained is quite good (i.e. 71% and 76%).

Table 4: Multiple regression model (cross-sectional time-series)
Fixed-effects option with analytical weight assumed
Europe from 2000 to 2007

VARIABLES	(A) Clinical Studies *(continuous variable)*	(B) Clinical Studies *(continuous variable)*	(A) Research Index	(B) Research Index
European Union	1.501***	1.504***	1.551***	1.570***
	(0.243)	(0.244)	(0.362)	(0.363)
Euro	1.323***	1.329***	1.213***	1.236***
	(0.147)	(0.147)	(0.218)	(0.218)
Population	21.88***	21.85***	27.71***	27.36***
	(2.934)	(2.963)	(4.366)	(4.407)
Wealth Index	3.515***	3.534***	6.928***	7.003***
	(1.073)	(1.073)	(1.596)	(1.596)
Physicians	0.00491*	0.00497*	0.00772*	0.00804*
	(0.00293)	(0.00294)	(0.00436)	(0.00437)
Gross Enrolment Ratio *(secondary level)*	0.00531		0.0190	
	(0.00852)		(0.0127)	
Gross Enrolment Ratio *(> secondary level)*		0.00289		0.0125
		(0.00563)		(0.00837)
Constant	-93.19***	-92.94***	-134.5***	-133.1***
	(10.75)	(10.82)	(15.99)	(16.09)
F statistic (p value>F)				
F(6,179)	55.08	55.03	33.08	33.07
Prob > F	0.0000	0.0000	0.0000	0.0000
R-squared				
Within	0.6487	0.6484	0.5258	0.5258
Between	0.7080	0.7080	0.7560	0.7565
Overall	0.4250	0.4250	0.6251	0.6259
Observations	218	218	218	218
Number of countries	33	33	33	33

Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Even if the degree of each country is considered, the model is still able to support the main proposed thesis concerning countries' competitiveness concerning the price of clinical evidence. The result of patients' knowledge is different since it is positive, as well as not being statistically significant. An interpretation of this difference could be linked to a different approach to the experimental activity by European citizens. In other words, on average, people with higher knowledge tend to refuse experimental treatment but, the behavior of bigger countries (i.e. higher *population* weight) could be different from that of the smaller ones (i.e. lower *population* weight).

Taking the Number of National Clinical Trials (count variable) into account, the next table tries to support the same proposed thesis but changes the econometric model, that is to say, using a Poisson regression, both with a random-effects option and a fixed-effects one. According to Hilbe (2011), the Poisson regression is the standard or base count response regression model, especially if there is no natural denominator (i.e. no limits on how large an observed count can be). In other words, assuming a Poisson distribution of clinical studies, the proposed model is the consistent one to explain the number of occurrences, or counts, of an event (i.e. the start of an experimental clinical activity). The choice

of this model is affected by the possibility to analyze the number of innovative medical treatments that have started in a country through a maximum likelihood estimation method.

Table 5: Poisson regression model (cross-sectional time-series)
Random-effects option
Europe from 2000 to 2007

VARIABLES	(A) Clinical Studies *(count variable)*	(B) Clinical Studies *(count variable)*
European Union	-0.0560	-0.0642
	(0.0605)	(0.0605)
Euro	0.860***	0.860***
	(0.0507)	(0.0506)
Population	1.258***	1.285***
	(0.323)	(0.327)
GDP on PPP	5.077***	5.077***
	(0.125)	(0.124)
Physicians	0.000334	0.000250
	(0.000645)	(0.000646)
Gross Enrolment Ratio *(secondary level)*	-0.00474***	
	(0.00139)	
Gross Enrolment Ratio *(> secondary level)*		-0.00430***
		(0.000993)
Constant	-50.27***	-50.41***
	(1.606)	(1.597)
lnalpha	1.268***	1.268***
	(0.200)	(0.200)
F statistic (p value>chi2)		
Wald chi2(6)	4324.98	4318.08
Prob > chi2	0.0000	0.0000
chibar2(01)	5260.99	5265.77
Prob >= chibar2	0.0000	0.0000
Pseudo R-squared	0.7657	0.7665
Observations	234	234
Number of countries	33	33

Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Table 6: Poisson regression model (cross-sectional time-series)
Fixed-effects option
Europe from 2000 to 2007

VARIABLES	(A) Clinical Studies *(count variable)*	(B) Clinical Studies *(count variable)*
European Union	1.464***	1.460***
	(0.0562)	(0.0562)
Euro	1.280***	1.268***
	(0.0507)	(0.0507)
Population	16.76***	17.07***
	(0.947)	(0.949)
Wealth Index	1.209***	1.103***
	(0.318)	(0.318)
Physicians	0.00655***	0.00627***
	(0.000670)	(0.000673)

Gross Enrolment Ratio *(secondary level)*	-0.0113***	
	(0.00134)	
Gross Enrolment Ratio *(> secondary level)*		-0.00871***
		(0.000949)
F statistic (p value>chi2)		
Wald chi2(6)	2827.52	2836.60
Prob > chi2	0.0000	0.0000
Pseudo R-squared	0.6478	0.6494
Observations	234	234
Number of countries	33	33

Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

According to the proposed thesis, taking a likelihood estimator into account, the most interesting explanatory variable is the proxy of physicians' fee (i.e. GDP on PPP and Wealth Index). Taking panel data into account, the analysis suggests that the higher the countries' economic growth, the higher the response in terms of clinical studies. Obviously, the higher growth will be where the main cost is more competitive (i.e. labor cost). Another interesting result is the negative prediction of research subjects' knowledge (i.e. GER), as well as the positive one of countries' population and Euro adoption.

All these results are consistent with the previous models as well the proposed theory. Moreover, the pseudo R-square indexes are good in both models, that is to say, taking the model into account, the hypothesis that there is a lack of fit can be rejected.

The last analysis is aimed to show European background with a *pooled* approach. In other words, taking population as analytical weight and the representative index of countries' wealth into consideration (but not the year), some dichotomous variables, one for each country, are assumed. Austria is dropped, that is to say, moving from Austria to another of the 32 European countries how could the Research Index and the national Clinical Studies change? Table 7 shows the results achieved.[21]

Table 7: Multiple regression model
Europe (Austria dropped)

VARIABLES	A **Research Index**	B **Research Index**	A **Clinical Studies** *(continuous variable)*	B **Clinical Studies** *(continuous variable)*
GDP on PPP	7.951***	6.322***	6.159***	4.959***
	(0.353)	(0.376)	(0.193)	(0.182)
Belgium	2.093***	1.995***	0.972***	0.895***
	(0.498)	(0.432)	(0.303)	(0.231)
Bulgaria	8.709***	6.485***	7.232***	5.620***
	(0.713)	(0.670)	(0.412)	(0.336)
Croatia	3.482***	2.089***	3.824***	2.811***
	(0.696)	(0.538)	(0.415)	(0.277)
Cyprus	-7.130***	-7.473***	-2.224*	-2.474***

[21] A category variable (i.e. country) had to be dropped because of collinearity and the choice of that country has been made by the STATA software, making the regression. The dropped country is the base category against which the others are assessed. See Suits (1957).

	(2.110)	(0.589)	(1.184)	(0.297)
Czech Republic	4.657***	3.750***	3.395***	2.739***
	(0.536)	(0.479)	(0.321)	(0.251)
Denmark	0.0593	0.0337	-0.124	-0.149
	(0.590)	(0.431)	(0.359)	(0.231)
Estonia	3.783***	2.447***	3.838***	2.875***
	(1.018)	(0.530)	(0.614)	(0.273)
Finland	0.947	0.752*	0.493	0.352
	(0.597)	(0.433)	(0.363)	(0.232)
France	3.649***	3.479***	1.570***	1.438***
	(0.399)	(0.433)	(0.243)	(0.232)
Germany	4.468***	4.312***	1.761***	1.643***
	(0.392)	(0.433)	(0.239)	(0.232)
Greece	0.633	0.0939	1.255***	0.865***
	(0.505)	(0.449)	(0.305)	(0.238)
Hungary	6.154***	4.922***	4.699***	3.797***
	(0.565)	(0.516)	(0.336)	(0.268)
Iceland	-7.131***	-7.147***	-2.989**	-2.998***
	(2.020)	(0.431)	(1.230)	(0.231)
Ireland	-3.172***	-3.024***	-1.761***	-1.657***
	(0.659)	(0.432)	(0.401)	(0.231)
Italy	3.693***	3.409***	1.849***	1.627***
	(0.403)	(0.436)	(0.245)	(0.233)
Latvia	4.845***	3.123***	5.043***	3.803***
	(0.864)	(0.586)	(0.515)	(0.298)
Lithuania	5.205***	3.606***	4.787***	3.641***
	(0.760)	(0.567)	(0.451)	(0.289)
Luxembourg	-17.05***	-15.71***	-8.844***	-7.864***
	(2.303)	(0.611)	(1.331)	(0.311)
Macedonia	4.890***	2.436***	5.787***	3.994***
	(1.078)	(0.733)	(0.632)	(0.367)
Malta	-4.053*	-4.752***	-0.915	-1.426***
	(2.437)	(0.552)	(1.409)	(0.284)
Netherlands	1.241***	1.292***	0.267	0.303
	(0.457)	(0.431)	(0.279)	(0.231)
Norway	-3.628***	-3.103***	-2.480***	-2.098***
	(0.632)	(0.448)	(0.384)	(0.238)
Poland	8.844***	7.298***	6.210***	5.088***
	(0.529)	(0.560)	(0.308)	(0.287)
Portugal	2.615***	1.785***	2.538***	1.916***
	(0.530)	(0.472)	(0.320)	(0.249)
Romania	9.283***	7.070***	7.590***	5.988***
	(0.648)	(0.668)	(0.370)	(0.335)
Slovakia	4.970***	3.665***	4.154***	3.220***
	(0.652)	(0.526)	(0.388)	(0.271)
Slovenia	-2.808***	-3.372***	0.0275	-0.373
	(0.949)	(0.483)	(0.568)	(0.254)
Spain	3.770***	3.410***	2.075***	1.806***
	(0.416)	(0.439)	(0.252)	(0.234)
Sweden	0.914*	0.826*	0.458	0.392*
	(0.515)	(0.432)	(0.313)	(0.231)
Switzerland	-0.292	-0.164	-0.721**	-0.627***
	(0.543)	(0.432)	(0.331)	(0.231)
Turkey	7.552***	5.586***	6.292***	4.856***
	(0.582)	(0.626)	(0.334)	(0.317)
United Kingdom	3.236***	3.116***	1.323***	1.231***
	(0.398)	(0.432)	(0.243)	(0.231)
Constant	-82.74***	-65.82***	-60.14***	-47.65***
	(3.685)	(3.917)	(2.020)	(1.898)

F statistic (p value>F)				
F	87.03	103.80	59.31	75.95
Prob > F	0.0000	0.0000	0.0000	0.0000
	F(33,213)	F(33,213)	F(33,246)	F(33,246)
Observations	247	247	280	280
R-squared	0.931	0.941	0.888	0.911
Mean VIF	4.00	2.85	3.76	2.66

Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

To avoid problems of collinearity, the analysis considers only the gross domestic product based on purchasing-power-parity per capita (GDP on PPP) as an explanatory variable. Considering the number of dichotomous variables, the mean of variance inflation factors are acceptable for both regressions. Moreover, a normal probability plot of standardized residuals has been verified with pretty good results.

What is really interesting is the difference between Eastern and Western Europe indicated in Table 6, especially comparing countries such as Romania and Bulgaria with Germany or France[22]. According to the paper's assumptions, the difference in growth in national clinical research could easily be explained by the cheaper fee necessary to involve physicians in the trial.

Regression (1) considers population as an analytical weight whereas (2) takes no weight into account. This can also show the different impact of population on countries.

Conclusion

According to the proposed thesis, human experimentation is ruled by economic forces. A statistically significant conclusion can be confirmed by data, that is to say, both the multiple regression model and the Poisson regression model can support the hypothesis of countries' competitiveness on physicians' fee. On one side the pharmaceutical industry wishes to test a new drug, on the other patients want medical treatments. In the middle, between these parties, there are physicians with their fees. This is the key to interpret the imperfect market of human experimentation. The price paid by companies for the required information is the physicians' fee instead of drug effectiveness. Moreover, what affects physicians' demand, affects national clinical research, that is to say, the necessity of a framing strategy and the degree of an alternative income.

In any case, are some physicians really profit machine? We are not certain about this, but it is true that there is an economic link between clinical trials and countries' economic conditions. We have assumed that the physician's fee is the main cost in the pharmaceutical testing phase. Could the absence of other costs, such as laboratory tests and specialist exams, belittle the proposed theory? As long as the weight of physicians' fees on the research subject's total cost continues to be higher than others, the hypothesis suggested works. Unfortunately, statistical analysis is affected by data availability and it is not easy to collect this sensitive information from pharmaceutical industries as well as public

[22] With regard to national performance, CeNGEPS was set up in France (28/03/2007). The *"Centre National de Gestion des Essais de Produits de Santé"* is a specific agency whose mission is *"maintenir l'attractivité du territoire français pour la réalisation des essais cliniques à promotion industrielle"*. See: http://www.cengeps.fr/.

institutions. However, the idea that behind a physician and a relative clinical trial there are not only scientific purposes but also economic interests is not compatible since the "…very word, "profit" is a signal that denies trust relations…"[23].

Taking physicians' economic interest into account, a policy maker's strategy to increase the national component of clinical research could be to link their careers to this factor instead of others. This kind of policy should shift the physicians' interest from pharmaceutical fees and increase the country competitiveness.

Of course there is also another path: if the values of society recognized research as a supreme value, as well as patients' well-being, the physicians' fee required would be equal to zero and the effectiveness protection system would be shaped around these medical researchers. To put it another way, social recognition would be the reward of their actions and patients' state of health would be the first real goal of these physicians and a protection system would be useless.

The interests of all parties involved are satisfied from this prospective. As long as the expected effectiveness behind experimental treatment is higher than the current one, pharmaceutical companies will develop trials in the country that is more competitive than the ones without these values. Obviously, in order to have this, it is necessary that people to appreciate this at its true value, that is to say, society has to invest to educate people and make them aware of this issue. Imagining values replacing ability, the policy maker's activity should be aimed at replacing current values with the proposed ones through an appropriate social policy.

In any case, the only aim of this paper is to show a potential path. The choice, as well as debates about connected risks and society's values, is the responsibility of the public stakeholder and not part of this discussion.

Obviously, the open issues of this work are due to the sample considered and the relative statistical assumptions. One of the limits is linked to the assumption that the analyzed sample of pharmaceutical companies is representative of the population of pharmaceutical companies (i.e. the pharmaceutical industry). At the same time, the localization of clinical research could also be affected by the development of the health care system. However, considering data availability, only some studies on each single country can suggest the appropriateness of this point. Other opportunities to develop this work could be linked to the validation of some hypothesises, such as the discrimination of physicians' fee among countries in a multinational studies, as well as the hypothesis that the sample of patients in a multinational study is equally shared among different locations. However, these could sound more like opportunities to further develop this work rather than admitting that a real limit of the proposed analysis exists.

Further empirical studies will deal with a micro reality, that is to say, within a specific country focusing both on physicians and the medical centres in which trials are conducted. The goal will be to understand how deeply the economic incentive affects performances of medical researchers introducing the degree of "physicians' fee" in the econometric models. Another study could focus on medical centers' competitiveness based on the expected cost of performing clinical researches, within the national market of human experimentation. Through an appropriate Data Envelopment Analysis, the hypothesis of the positive relationship between the efficiency of the medical center (on the cost side) and the localization of the clinical trial could be supported with interesting results. In addition another future project will be to study the potentiality of the protection system of patients' rights on the proposed market and how it could affect pharmaceutical companies' strategies.

[23] Arrow (1963) suggests "…one consequence of such trust relations is that the physician cannot act, or at least appear to act, as if he is maximizing his income at every moment of time…"

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