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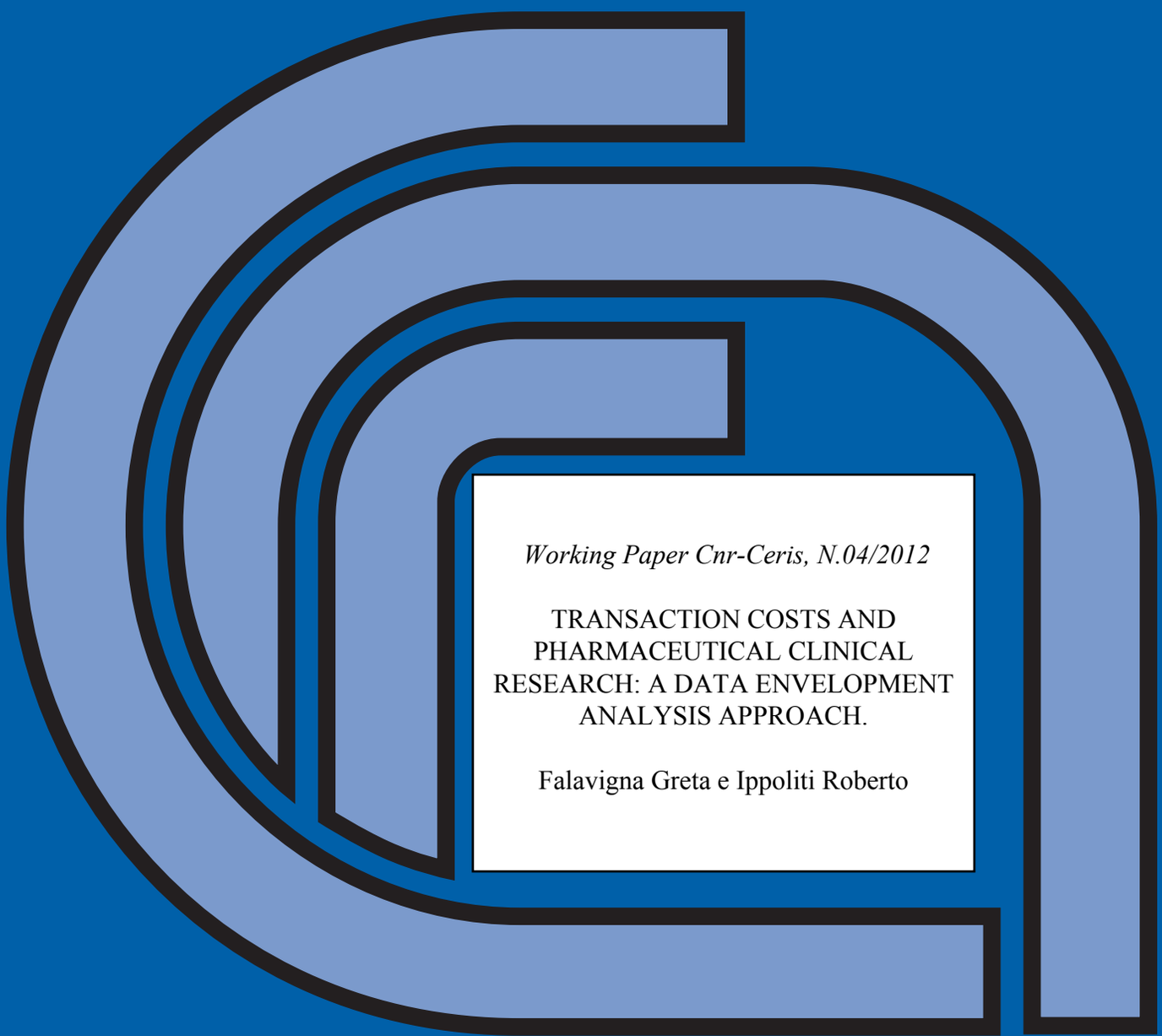

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TRANSACTION COSTS AND PHARMACEUTICAL CLINICAL RESEARCH: A DATA ENVELOPMENT ANALYSIS APPROACH.

Falavigna Greta e Ippoliti Roberto

Working Paper

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Transaction costs and pharmaceutical clinical research: a Data Envelopment Analysis approach.

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ABSTRACT: Taking human experimentation into account, this work aims at estimating the relationship between transaction costs, which are related to the protection system of patients' rights, and localization of pharmaceutical industry's testing phase. Assuming that the competitiveness of the protection system is based on the time required to obtain an authorization for an experimental activity, pharmaceutical clinical research should be positively affected by a process aimed at internalizing the review process, if efficient. By analyzing said system with operational research, this paper concludes suggesting the potentiality of a competitive system of reviewers, that is to say, the efficiency of that internalization process is performed by medical centers in which the experimental treatments are proposed to subjects.

Keywords: Transaction costs; International Review Boards (IRB); Medical researcher; Research subject; Clinical research

JEL Codes: I18, L51

SUMMARY

1. THEORETICAL BACKGROUND

The concept of transaction costs has been introduced by Coase (1937), studying firms and market organization. However, as suggested by Coase himself (1988), the assumption of positive transaction costs, instead of zero costs, has only begun to take hold after two decades. This turning point is due to two contributions (Coase, 1960; Arrow, 1969) in which the necessity to study the real world of positive transaction costs and the failure of many current theories is underlined.

In the following years, the idea of positive transaction costs was deeply analyzed, especially in the field of governance, i.e. how activities and exchanges are appropriately, or inappropriately, organized to minimize these positive transaction costs. As suggested by Wlliamson (2009) in his Nobel Prize lecture, "…governance is the overarching concept and transaction cost economics is the means by which to breathe operational content into governance and organization…". In other words, a strong link between transaction costs and organization, as well as governance, exists and the importance of the topic is demonstrated by the Nobel Prize winner. Wlliamson's work on issues of governance (1979, 1996, 2002, 2008), as suggested by Figueiredo (2010), has a significant impact on several fields, including the development of public organization.

Starting from their analysis, this paper aims at empirically studying a specific public sector and the impact of an internalization process geared towards reducing the transaction costs that might prevent an exchange of innovation for information. This specific exchange can affect the regions' competitiveness on a particular kind of national market: the market of human experimentation. The specific public sector of this analysis is the protection system of research subjects, which is mainly based on Institutional Review Boards (IRB). According to Calabresi (1969), these IRBs are the institutions through which society can evaluate the acceptable risk of killing someone for the sake of scientific progress, since they represent the moral values of these cultures. Currently, both in Europe and in the U.S., the protection systems of patients' rights are guaranteed by these boards and this analysis is performed around them. Referring to the idea of Arrow (1963) about the medical care market, Ippoliti (2010) suggests the existence of a specific sub-market 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 abovementioned exchange, as well as the competitiveness of countries. This competitiveness is based on transaction costs, that is to say, 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.

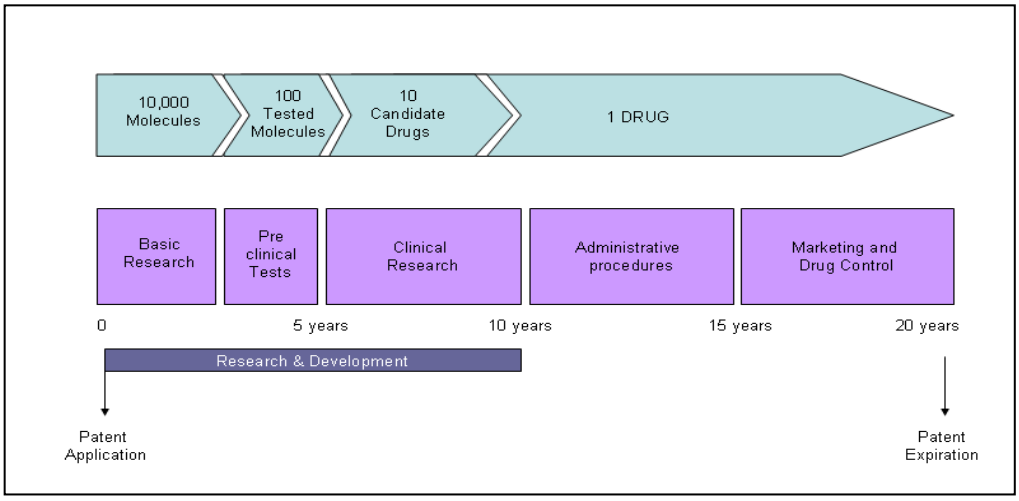
Considering the proposed background and through Operational Research (OR), this paper analyzes if the review process should be internalized within the medical centers, in which the experimental activity is performed, or not. In other words, the paper studies if this internalization process is more or less efficient. It will also suggest some conclusions that public stakeholders may find relevant: a normative analysis of the protection system of patients' rights, investigating how an optimal protection system might be shaped in order to be competitive.

The paper is divided in three sections. The second section describes the nature of transaction costs within the realm of human experimentation, while also presenting the legal background around which the specific national case study is shaped. Through Data Envelopment Analysis (DEA), the third section presents an operational research to achieve the main target of this work. The paper concludes with some remarks, considering the public stakeholders' point of view and the potential political influence on the decision of creating an efficient protection system of patients' rights.

2. TRANSACTION COSTS AND HUMAN EXPERIMENTATION

Currently, human experimentation is related to pharmaceutical clinical research. We are talking about the testing phase of candidate drugs in order to collect clinical evidence about experimental treatments. This information is essential to obtain manufacturing authorization from national drug agencies and thus to make profit on patients and their diseases. In other words, before the manufacturing of the drug, it is necessary to know how effective we can expect the product to be. However, manufacturing authorization is not the only *ex-ante* check. Human experimentation can be considered the realm of *ex-ante* regulation: each clinical research has to be authorized by an IRB before starting the testing phase of the experimental treatment on patients. Obviously, the need for a strong regulation system is clearly affected by the specific technical knowledge necessary to evaluate if the expected and unexpected risks are acceptable or not, as well as the scientific rationale of the proposed trial.

Figure 1: Production process of the pharmaceutical industry



Source: Les Entreprises du Médicament (LEEM)[*]

*For a deeper analysis see the LEEM report entitled "L'industrie du médicament en France, réalités économiques", 2008 Edition.

Figure 1 shows the pharmaceutical companies' production process. What we are interested in is clinical research, which is exactly the abovementioned testing phase of innovative treatments. Considering the protection system of patients' rights, we can imagine that the key factor in this specific phase is the time needed to obtain an opinion about the experimental use of these candidate drugs on patients. Decreasing the time this phase takes means maximizing the expected profit in the marketing phase. In other words, one day saved in the bargaining process to obtain an authorization means one day gained to sell the drug on the market with monopolistic power. For this reason, we can talk about the required time to obtain an authorization as the main price of starting an experimental treatment and the collection of clinical evidence.[1]

According to the literature mentioned in the previous section, transaction costs can be thought of as the costs of an exchange. Referring to the idea of human experimentation in terms of market, an exchange of clinical evidence for innovation in medical treatments is foreseeable. However, due to the ex-ante control that is performed by IRBs, there is a cost (i.e. a positive transaction cost) that companies have to bear in order to perform this exchange: the cost of obtaining the ethical opinion on this innovative treatment. According to what has been presented in the profit maximization process of the pharmaceutical industry, the key factor of the authorization process is the time needed to obtain that opinion, that is to say, the time necessary to perform the exchange between companies and patients. Cooter and Ulen (2000) suggest that there are three main potential transaction costs corresponding to the three steps of an exchange: search costs, bargaining costs, and enforcement costs. The bargaining phase is the main cost involved in this specific phase of the pharmaceutical industry's production process. Indeed, a negotiation in the authorization process between companies and IRBs is foreseeable. For example, one of the main negotiations could deal with the informed consent, i.e. the main risks (expected and unexpected adverse events) that have been included in that document. This is essentially to estimate the degree of risk sharing among the parties since research subjects are responsible for all the expected adverse events that are included in the informed consent whereas companies bear all the unexpected ones.[2]

According to the European Union's directives on human experimentation and protection system of patients' rights (2005/28/EC and 2001/20/EC), in Europe

[1] Clinical trials are conducted in phases. Each phase has a different purpose and helps scientists answer different questions. For each step of this clinical investigation, a specific ethical opinion must be provided by the competent IRB. In details, there are three phases in pharmaceutical clinical research with, according to the National Health Institute, the following features: "…Studies of phase I in which researchers test an experimental drug or treatment on a small group of healthy people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects... in phase II trials, the experimental study drug or treatment is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety… in phase III trials, the experimental study drug or treatment is given to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the experimental drug or treatment to be used safely…".

[2] From this prospective, the Informed Consent can be seen as a contract between companies and patients. Upon signing the contract, research subjects become responsible for all the expected risks listed in the document. Obviously, note that all adverse events that are not included in the Informed Consent could be potential unexpected ones. For this reason, the bargaining on this information might be significant. For a deeper analysis of this issue, see Ippoliti (2010).

each protocol has to be authorized ex-ante by a competent IRB. However, these directives have been integrated by each European country into national law with different features regarding the governance of these IRB systems. For instance, there are countries that have decided to adopt centralized systems (e.g. Croatia and its single national IRB), regional systems (e.g. France and its departmental system) or local systems (e.g. Italy and its local network of IRBs). Another issue concerns the requirement of a single opinion, rather than two. The European Directive suggests that pharmaceutical companies' experimental protocols can be evaluated with a single opinion by a competent national IRB. Afterwards, that single opinion can be extended to all the country's medical centers.[3] Also in this case there are national differences in the adoption of the Directive. Indeed, some countries (e.g. Italy) have decided to accept the single opinion but with a procedure of accepting/refusing that opinion by all competent IRBs involved in the authorization process (i.e. second opinion). Anyway, how do national choices in adopting the European Directives affect transaction costs? Coase's theorem suggests that the law can encourage bargaining by lowering transaction costs (Coase, 1960). According to his idea of market, this should be exactly the final target of this process in order to increase the pharmaceutical companies' investments in the testing phase (i.e. the exchange among companies and patients).

The two examples mentioned above will be relevant for the proposed analysis, since it focuses exactly on these key factors to estimate the relationship between clinical research and transaction costs, and to validate the idea of transaction costs applied to human experimentation.

In Italy, the European Directives on human experimentation have been acknowledged with the *Ministerial Decree of 06/11/2007* and *Legislative Decree no. 211 of 24/06/2003*. According to these laws, the Italian protection system includes a single opinion by the *coordinator* medical center and then a second opinion by each IRB competent for the *satellite* medical centers. This second opinion can accept, or not, the previous single opinion of the coordinator center. This is a specific feature of the Italian IRB system since, as mentioned above, the European Directive suggests that a single opinion should be valid for the whole country, without needing a second opinion by the satellite centers. Moreover, within the Italian governance, each region is entrusted with organizing and setting up a local network of IRBs (i.e. 21 competent authorities). This creates a system of 21 regional networks of IRBs with common features, as well as differences like, for instance, the administrative procedures to obtain the ethical opinions. Obviously, the exchange between the pharmaceutical industry and patients could be affected negatively only by the combination of these two features (i.e. local system and second opinion).[4] The awareness about the Italian difficulties on the European market of human

[3] In case of a negative single opinion, the trial cannot be proposed in that country again. Alternatively, the Directive suggests the possibility of obtaining an opinion from each territorially competent IRB.

[4] The average time the coordinator of an Italian Institutional Review Board takes to come to a decision is 35 days, while the satellite takes 50 days. Considering also that the authorization from the institution where the trial is conducted takes time, this means that it usually takes at least 4 months before an exchange can be performed. See AIFA, *La sperimentazione clinica dei medicinali in Italia, 8° Rapporto Nazionale, 2009.*

Table 1: Protection system of patients' rights
Italy, 2007

Region	Population/IRB	IRB	Population
Umbria	878709	1	878709
Piedmont	625292	7	4377047
P.A. of Trento	510194	1	510194
Emilia Romagna	472170	9	4249533
Veneto	436632	11	4802947
Puglia	313324	13	4073208
Toscana	281356	13	3657630
P.A. of Bolzano	245396	2	490792
Campania	232032	25	5800789
Abruzzi	219482	6	1316892
Italy	*219097*	*271*	*59375295*
Marche	171620	9	1544581
Lazio	167490	33	5527163
Sardinia	166253	10	1662530
Liguria	160885	10	1608850
Molise	160228	2	320456
Lombardy	157277	61	9593924
Sicilia	156977	32	5023272
Calabria	154068	13	2002880
Friuli Venetia Giulia	152167	8	1217332
Basilicata	147793	4	591170
Valle d'Aosta	125396	1	125396

Sources: AIFA and ISTAT

experimentation is probably the main reason that led to the *Ministerial Decree of 12/05/2006*. Indeed, the idea behind this reform is the harmonization of all the different administrative procedures to obtain an ethical review, in order to achieve a considerable decrease in the time needed by IRBs to provide their opinions. However, this harmonization process might be only one positive input, among several others, to increase the Italian competitiveness on the European market of human experimentation.

In the next section the paper presents data and methodology applied to the Operational Research.

3. ITALIAN IRB SYSTEM

Taking 2007 into account, there are 271 Institutional Review Boards (IRB) in Italy. Table 1 shows that, on average, there are 219,097 citizens for each IRB in Italy but this number changes within each region. Indeed, the Italian protection system is shaped around a regional network of IRBs. For instance, the region of Umbria has only 1 IRB whereas the region of Piedmont has decided to develop this network of protection system based on 7 IRBs. In any case, both regional systems are shaped around a limited number of IRBs depending on their population, as described in table 1.

Table 2: Poisson regression model (cross-sectional time-series with fixed-effects option) Italy, from 2000 to 2007

VARIABLES	(*count variable*) Number of IRB	(*count variable*) Number of IRB	(*count variable*) Number of IRB
Medical centers	0.109***		
	(0.0360)		
Clinical studies		0.0873***	
		(0.0276)	
Research Index			0.0961***
			(0.0311)
Law reform	-0.151**	-0.148**	-0.130*
	(0.0709)	(0.0700)	(0.0682)
F statistic (p value>chi2)			
Wald chi2(2)	10.17	10.98	10.52
Prob > chi2	0.0062	0.0041	0.0052
Observations	8	8	8
Number of Countries	1	1	1

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

Other regions, such as Friuli Venetia Giulia and Basilicata, have opted for a higher number of IRBs.

The idea of a local protection system is consistent with the authorization process of experimental protocols, since a double authorization is necessary (the opinion of the IRB competent for the coordinator center and the second opinion of each local IRB). According to this rule, each regional policy about the protection system of patients' rights is affected by the demand of clinical evidence by pharmaceutical companies. In other words, the main regional policy is as follows: the higher the number of experimental protocols, the higher the number of IRBs to evaluate these trials.

Table 2 shows the positive link between the supply of innovative medical treatments and the number of local IRBs, as well as the impact of the law reform on this value. The proposed model is a Poisson regression, cross sectional time-series, applying the fixed-effects option. Data about the number of IRB are extracted from the annual report of the Italian Drug Agency (AIFA)[5], whereas data about the dependent variables are medical centers, clinical studies[6] and a Research Index (Ippoliti, 2011b). These variables are extracted from the National Institute of Health (NIH) and in particular medical centers are the medical care facilities where experimental treatments are performed, whereas clinical studies are exactly those innovative treatments.

[5] The reports analyzed to estimate the protection systems of patients' rights refer to the period from 5/2006 to 8/2009. These reports can be downloaded from the Drug Agency's website: http://www.agenziafarmaco.gov.it/ .

[6] This work considers all clinical studies of phase II and III funded by the Industry.

The Research Index is a combination of medical centers and clinical studies, which might be able to catch the national competitiveness on the market. This index represents a good proxy of pharmaceutical investments in Europe and, therefore, countries' competitiveness on the European market of human experimentation.

The *deviance goodness-of-fit* test is acceptable and, considering the resulting chi2 p-value, the models are considered well fitting. Moreover, even if only 1 country is considered for 8 years, the result is statistically consistent with both the number of medical centers and the number of clinical studies, as well as with the Research Index.

The table supports the common policy followed by all regions in this specific field, i.e. the higher the number of trials, the higher the number of IRBs internalized in the medical facilities where the trials are performed. At the same time, the table shows the impact of the law (i.e. *Ministerial Decree of 12/05/2006*) on the number of IRBs. According to the reform, a specific setup of the IRBs is required (i.e. minimum requirements about the boards' composition). This means that, between 2006 and 2007, 37 IRBs did not pass the validation process linked to these requirements and this is why Table 2 presents a negative coefficient in all three regressions (i.e. law reform). However, the reduction of local IRBs has not been the target of that law, but only an indirect consequence of that measure.

The issue is the following: is the internalization of the review process efficient? In other words, is a high or a low number of reviewers more efficient? Which might be the best regional policy in the shaping of local networks of IRBs?

The next sub-sections try to provide an answer to this efficiency question performing an OR. Obviously, in order to suggest a consistent explanation, a study of the local situation instead of an international one is necessary. Hence, a national data-set is used.

The analysis of health care systems' performance through an OR study is not new. The current bibliography suggests several innovative applications of OR in Health, at both a regional and a national level, focusing on quality and quantity of supplied medical goods (Pulina *et al.*, 2010; Piacenza *et al.*, 2010; Zuckerman *et al,* 1994; Garavaglia *et al.,* 2011). Considering pharmaceutical clinical research, an OR study is proposed by Ippoliti and Falavigna (2011). The authors support the thesis that there is a positive relation between patients' perception of expected quality of medical treatments and regional supply of pharmaceutical innovation (i.e. experimental drugs). The nature of the Italian regional system makes it possible to develop an OR to estimate the efficiency relationship between the local network of protection systems (i.e. number of IRBs) and the regional supply of innovative medical treatments. Further analysis can increase the current knowledge of OR studies in health care and enhance the positive perspective of this work.

Table 3: Descriptive statistics of efficiency scores, output and inputs (mean on 2005-2008)

Type	Variable	Obs.	Mean	Std. Dev.	Min	Max
Inputs	Physicians	84	5049.06	3788.803	278	13017
	Ambulatory Activity	84	3.51e+07	3.28e+07	886825.7	1.18e+08
Outputs	Clinical studies	84	91.97619	76.55772	0	311
	Medical centers	84	148.1548	162.8274	0	713
Efficiency scores	Score 1	83	2.569687	2.405073	1.163342	15.27147
	Score 2	83	3.233914	2.999152	1.164434	21.54154
	Score 3	83	2.549812	2.320114	1.177682	15.32819
Independent variable	Population on IRBs	84	12.28024	0.584946	11.0302	13.6982

3.1 Data and methodology

The methodology applied in this work to estimate efficiency is the Data Envelopment Analysis (DEA).[7] According to Cook and Seiford (2009), the DEA approach is a non-parametric technique which allows us to measure the performance of a subject and to assign a score to it representing its efficiency performance. The two-stage procedure of Simar and Wilson (2007) is performed, i.e. the first approach (DEA scores) is followed by a second approach in which these scores are regressed for some key factors to explain the regions' efficiency. In the first stage, the DEA output-oriented procedure with bootstrap is used to estimate the efficiency of each regional medical care industry and its supply of innovative medical treatment; in the second stage, the regression analysis aims at showing the correlation between efficiency scores and national protection system.

The sample is made up of 19 Italian regions plus 2 autonomous provinces and the considered panel is from 2005 to 2008. Obviously the choice of years is affected by data availability. The output is the pharmaceutical clinical research, considering all studies of phase II and III funded by the Industry and started in Italy. Based on the previous analysis, both the number of medical centers and the number of clinical trials will be considered, as well their combination. Inputs are the number of physicians and the access of patients to the regional ambulatories (clinical and diagnostic). The proposed idea of efficiency concerns the regions' ability to maximize the supply of innovative medical treatments (output) considering the regional potential in the enrolment of research subjects

[7] The DEA approach allows us to build a deterministic non-parametric production frontier comparing the performances of several Decision Making Units (DMUs). Technical efficiency scores are calculated on the basis of the radial distance of the subjects to the frontier. A comprehensive description of this approach is presented by Charnes *et al.* (1978), Färe *et al.* (1994) and Coelli *et al.* (1998).

(inputs).[8] Table 3 introduces descriptive statistics of inputs and outputs, as well efficiency scores and the independent variable.[9] Score 1 considers clinical studies as output whereas score 2 regards the medical centers in which those trials are performed. Score 3 is a combination of both outputs, that is to say the DEA approach using two outputs instead of one.

Data about clinical research (Clinical studies and Medical centers) are extracted from the dataset of the Italian Drug Agency (AIFA), whereas data about inputs are extracted from the reports of the National Health Care System (SSN)[10] and refer to the public health care system.

In the next section the second stage of Simar and Wilson is proposed.

3.2 Results

According to Simar and Wilson (2007), in the second stage the efficiency scores are regressed to explain the results. Considering Italy between 2005 and 2008, a multiple regression model is proposed in Table 4. It is a cross sectional time series regression model, applying the random effects option. In this case we assume that there are no significant statistical differences between one region and another. Also in this case the parameters are tested to validate the required assumptions (i.e. normality distribution and residuals) with acceptable results.

The dependent variables are the efficiency scores of the previous section, whereas the independent variables are the regional population on the number of IRBs (see Table 1) and all regions (i.e. a dummy variable to identify each region). Considering all regions, their regional protection system of patients' rights is ranked on the basis of efficiency. In other words, the table suggests how the trend of their efficiency can change moving from Umbria (dropped region) to another region.[11]

Note that, according to the DEA approach, a positive coefficient means a negative impact on efficiency scores whereas, obviously, a negative coefficient means a positive effect on the scores. The table empirically supports the idea that decreasing the number of IRBs for each potential research subject is not efficient, especially if the medical centers are considered. According to the proposed background, a process through which the review process is incorporated within the medical center in which the experimental activity is performed might be more efficient. In other words, increasing the number of reviewers decreases the transaction costs since, reasonably, the time necessary to perform an exchange between pharmaceutical companies and patients decreases. Indeed, if the companies' decision making process about locations (i.e. medical facilities) is affected by the

[8] According to Ippoliti (2010, 2011a), the enrolment process can be ascribed mainly to the relation between the physician and the patient, which can lead to the production of the required clinical evidence. This means that the number of physicians (workers) and the number of potential research subjects to whom these physicians might propose the experimental treatments (raw material), can be considered the basic inputs for this analysis.

[9] Note that one score has not been computed since the output oriented approach is used but for a region there are no clinical studies in 2006 (i.e. Valle d'Aosta).

[10] Data about clinical research can be downloaded from: http://oss-sper-clin.agenziafarmaco.it/; whereas data about inputs can be downloaded from http://www.salute.gov.it.

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

Table 4: Multiple regression model (cross-sectional time-series with random-effects option) Italy, from 2005 to 2008

VARIABLES	*Clinical studies* Efficiency Scores 1	*Medical centers* Efficiency Scores 2	*Both* Efficiency Scores 3
Population on IRBs	0.237**	0.326**	0.229**
	(0.110)	(0.137)	(0.111)
Piedmont	0.466***	0.824***	0.461***
	(0.131)	(0.165)	(0.133)
Valle d'Aosta	0.603**	0.682**	0.578**
	(0.273)	(0.343)	(0.276)
Abruzzi	0.314*	0.565**	0.305
	(0.188)	(0.236)	(0.190)
Basilicata	1.499***	1.577***	1.469***
	(0.231)	(0.289)	(0.233)
P.A. of Bolzano	2.252***	2.292***	2.150***
	(0.204)	(0.256)	(0.206)
Calabria	1.500***	1.744***	1.494***
	(0.228)	(0.285)	(0.230)
Campania	0.986***	1.352***	0.979***
	(0.188)	(0.235)	(0.190)
Emilia Romagna	0.171	0.337*	0.192
	(0.163)	(0.204)	(0.165)
Friuli Venetia Giulia	0.503**	0.571*	0.477**
	(0.239)	(0.299)	(0.241)
Lazio	0.387*	0.385	0.402*
	(0.224)	(0.281)	(0.227)
Liguria	0.340	0.411	0.327
	(0.223)	(0.280)	(0.226)
Lombardy	0.383*	0.442	0.435*
	(0.225)	(0.282)	(0.228)
Marche	0.793***	0.962***	0.778***
	(0.237)	(0.297)	(0.239)
Molise	0.541**	0.619*	0.520**
	(0.256)	(0.321)	(0.259)
Puglia	0.949***	1.188***	0.939***
	(0.180)	(0.225)	(0.182)
Sicilia	1.087***	1.531***	1.072***
	(0.223)	(0.280)	(0.226)
Sardinia	0.879***	1.098***	0.870***
	(0.220)	(0.276)	(0.223)
P.A. of Trento	1.841***	1.861***	1.840***
	(0.137)	(0.172)	(0.139)
Veneto	0.591***	0.999***	0.581***
	(0.170)	(0.213)	(0.172)
Toscana	0.256	0.514**	0.260
	(0.179)	(0.224)	(0.181)
Constant	-2.980**	-4.023**	-2.860*
	(1.502)	(1.882)	(1.519)
F statistic (p value>chi2)			
Wald chi2(21)	875.68	603.28	809.44
Prob > chi2	0.0000	0.0000	0.0000
R-squared			
Within	0.0714	0.0846	0.0653
Between	1.0000	1.0000	1.0000
Overall	0.9349	0.9082	0.9299
Observations	83	83	83
Number of Regions	21	21	21

Standard errors in parentheses

*** p<0.01, ** p<0.05, * p<0.1

Umbria is the dropped region because of collinearity

time required to start a trial, in order to be competitive on the national market of human experimentation several medical institutions should adopt a policy aimed at internalizing this process. Even if it might be considered a *second best*, the results support the appropriateness of this policy, as clearly shown in Table 2.

There is a final question that has to be answered. Is this internalization (i.e. authorization process) an issue linked to transaction costs (i.e. trying to minimize the time to perform an exchange) or to the necessity to control the ethical judgment? In other words, is the internalization process an attempt to facilitate the exchange? The conclusions of this work deal with the policy maker's point of view. According to the empirical results and the Italian background, the last section presents a normative analysis in order to propose a potential optimal protection system, which however proves politically inapplicable.

4. CONCLUSIONS

A high number of competitors is an opportunity if an open market exists. This is the basic assumption of each potential competitive market and the regulation process of experimental treatments might be affected in the same way. Analyzing the issue in terms of public governance, a high number of reviewers might be an opportunity to shape a competitive market in the regulation process. Obviously, the final aim of this competitiveness can only be the minimization of transaction costs, i.e. the cost of the exchange between companies and patients. In other words, the higher the number of IRBs, the higher the pharmaceutical companies' degree of choice (of a reviewer); but this also means the boards have strong incentives to be efficient, minimizing the transaction costs. Of course, if a protection system is more competitive, the number of innovative medical treatments will increase with positive externalities on the health care system (i.e. medical options with expected higher effectiveness, as well as economic investments in the testing phase and physicians' training).

Nevertheless, a competitive market needs some other features to work. An appropriate system of economic incentive is necessary, i.e. a system that can guarantee the existence of IRBs thanks to the fee of each authorization. This is essential to provide an economic incentive to be competitive on the market and, at the same time, to minimize the economic burden of these institutions on public society. Another point is the territorial competence of each IRB. For what concerns the Italian system, a specific territorial area of competence might be seen as as a monopolistic power on the medical facilities that are in that area. Thinking in regional terms, each IRB could be competent for the whole region and, in this way, a regional competitive market of regulation would be created.

This is the normative analysis on how a protection system should be shaped, according to the current knowledge and supported by the interpretation of the Data Envelopment Analysis' results.

However, even if IRBs were autonomous from the medical centers in which the trials are performed, their institution, as well as the members' appointment, would be a decision of the general manager of those facilities.[12] Obviously, the members'

[12] According to the 5th Report of the Italian National Drug Agency (2007), 78% of Italian IRBs have been instituted by these general managers. Obviously, these managers are also competent for the appointment of IRBs' members, which is strictly related.

appointment is an opportunity to informally control the experimental activities, i.e. an opportunity to decide which medical researcher can perform, or not, a clinical trial. The tool to perform this unfair control could be, of course, the time needed to authorize a trial, i.e. the manipulation of transaction costs to perform an exchange between companies and patients. In other words, a trial in which the medical researcher has a friendly relationship with the management can be authorized, minimizing the expected transaction cost. At the same time, a medical researcher who is not on friendly terms with the management could be penalized, maximizing the expected transaction costs of an ethical decision. According to this approach, the protection system of patients' rights sounds more like a system of political control on the pharmaceutical clinical research performed in public medical facilities.

The political necessity to guarantee this unfair control might be the real cause of the failed reform of the authorization process (second opinion).

This hypothesis is even more consistent if we consider that the local network of protection and the appointment of general managers are of regional competence.

Based on these considerations, political influence is the real problem of Italian competitiveness on the market of human experimentation. Only if the political power leaves the current protection system free to compete for a single opinion, i.e. without the need to approve what another board has already approved, the impact on national competitiveness could be significant. This could really affect the pharmaceutical companies' decision making process about locations of clinical studies, thus leading to a higher expected supply of innovation in medical treatments.

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