Pharmaceutical clinical research and regulation: an impact evaluation of public policy

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Abstract:
Taking human experimentation into account, this work aims at estimating a policy designed to reduce transaction costs that are related to the protection system of patients’ rights, with both a normative and positive approach. On the one hand, considering a sample of European countries as counterfactual, an empirical analysis is performed in order to estimate the impact of a national law aimed at harmonizing the procedure to obtain opinions on clinical trials. On the other hand, an alternative law, which might be able to favor the exchange between pharmaceutical companies and patients, is proposed.
Assuming that the competitiveness of the national 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 reform of the current law. However, there is also evidence of a wasted opportunity to optimize the governance of the national protection system.

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

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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 Williamson (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. Williamson’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 a law reform geared towards reducing the transaction costs that might prevent an exchange of innovation for information. This specific exchange can affect the countries’ competitiveness on a particular kind of 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. According to Adobor (2011), regulation is a potential factor of
pharmaceutical companies’ localization of testing phase, especially considering the need for speed in drug development. Indeed, as suggested by Bodenheimer (2000), each day’s delay in gaining FDA approval of a drug, the manufacturer loses, on average, $1.3 million in potential revenue. Considering the proposed background, this is a specific topic in which the abovementioned literature can be applied to analyze and to validate, or not, an applied public policy aimed at harmonizing the procedure to obtain an ethical opinion, minimizing the costs required to start a clinical trial. At the same time, there are opportunities to assess the existence of potential gaps in the proposed reform, as well as the proposal of an alternative approach.

Emphasizing the time required starting a clinical trial, this paper has three main goals. The first, which is mainly an empirical goal, is linked to the impact of the public policy: is a law reform able to increase pharmaceutical clinical research? If the analysis gives positive feedback, this paper can support the hypothesis that the transaction cost is able to affect the bargaining (i.e. the idea of exchange between research subjects and companies) and the competitiveness of countries on the proposed market. The second is linked to assessing potential impact: is the proposed reform complete? In other words, is the law reform a wasted opportunity to lend significant impact to the governance of this specific public institution? If the law reform is non complete and, therefore, it is unable to boost national competiveness on the globalized market of human experimentation, then a third question arises. Which might be the reason behind this approach? Is it an absence of awareness?

The paper is divided in two 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. The third section shows the data and methodology applied, as well as it describes the main results of the empirical analysis to estimate the impact of the law reform and considers if the reform is complete or not. The paper concludes with some remarks about the law reform, 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 refer 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

![Diagram of the pharmaceutical industry's production process](Source: Les Entreprises du Médicament (LEEM))

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. Notice that the moment in which a

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4 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
pharmaceutical company takes out a patent, i.e. before the experimental treatment, affects the approach.

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.\(^5\)

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 each protocol has to be authorized ex-ante by a competent IRB.\(^6\) 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. Finland 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.

\(^5\) 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).

\(^6\) The European Directive has been applied by all European countries, i.e. both EU members and no members (e.g. Croatia, Switzerland, Norway, Turkey, Iceland and Macedonia).
Afterwards, that single opinion can be extended to all the country’s medical centers.\textsuperscript{7} 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 the next section, a specific case study is analyzed: a new national rule aims at harmonizing the procedure to obtain opinions on experimental treatments. Starting from a local network of IRBs, the law imposes strict regulations to “lubricate” the bargaining and, in this way, to be more competitive on the European market of human experimentation. The empirical analysis will show the effect of this reform, as well as the incompleteness of the reform, which results in a wasted opportunity to significantly increase the countries’ competitiveness.

3. Italian Law reform

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.\textsuperscript{8} 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

\textsuperscript{7} 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.

\textsuperscript{8} For instance, let us assume a clinical trial with 4 medical centers: one coordinator center and three satellite centers. According to the Italian rule, a single opinion from the coordinator center is necessary and, afterwards, other three second opinion from each competent IRB is necessary. The reader can see the National Monitoring Centre for Clinical Trials to explore this phenomenon: http://oss-sper-clin.agenziafarmaco.it.
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). The awareness about the Italian difficulties on the European market of human 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. In other words, others more significant inputs, not considered in this paper, can increase the Italian competitiveness on the European market of human experimentation. On the one hand, is the law able to achieve its target? On the other hand, considering the proposed background, is there another measure that might have a significant impact on the Italian competitiveness? In other words, is this reform complete or incomplete?

In the next sub-section the paper presents data and methodology applied to the empirical analysis in order to provide answers to these open issues.

3.1 Data and methodology

In order to estimate the impact of a law reform, a counterfactual analysis is necessary. In other words, a sample with treated and untreated observations is needed to estimate the trend of pharmaceutical clinical research and to assess the real impact of the Italian law reform. For this reason, an international panel data-set is proposed, considering European countries from 2000 to 2007. In this work, Europe is considered a group made up of 33 countries: EU-27 plus candidate states (Croatia, the Former Yugoslav Republic of Macedonia, Turkey), Norway, Switzerland and Iceland.

Data about dependent variables are extracted from the National Institute of Health (NIH) and they are proposed in several ways (i.e. continuous and count variables, as well as combinations of different values). This work considers all clinical studies of phases II and III funded by the Industry with at least one location in the considered sample of European countries. Obviously, a statistical assumption about pharmaceutical companies is necessary since we are working with American data

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9 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, *Laserperimentazione clinica dei medicinali in Italia, 8° Rapporto Nazionale*, 2009.

10 Studies of phase I are not considered since healthy subjects are enrolled, whereas studies of phase IV are post marketing trials to gather additional information including the drug's risks, benefits, and optimal use.
to study a European situation. The data extracted from NIH database are representative of the whole population of studies performed in Europe. In other words, the sample of pharmaceutical companies, from which the proposed dependent variables are derived, is representative of the whole population performing clinical research in those countries. This assumption is affected by data availability as well as by the necessity to have homogeneous data (i.e. an appropriate counterfactual analysis).

Considering that this paper tries to estimate the impact of a policy on the pharmaceutical industry’s testing phase, dependent variables have to represent this specific activity: *medical centers* and *clinical studies*. Medical centers are the medical care facilities where experimental treatments are performed, whereas clinical studies are exactly those innovative treatments. The proposal of several dependent variables allows estimating the impact of interesting explanatory variables on several key factors of the pharmaceutical industry’s testing phase. Both variables are proposed as count and as continuous variables to estimate the effect of the independent variables through different estimation models. At the same time, a combination of these two variables within a specific index (i.e. *Research Index*) is proposed. According to Ippoliti (2011), the Research Index is a combination of medical centers and clinical studies, which might be able to catch the national competitiveness on the market. In details, considering *n* countries (a subgroup of the potential *G* candidate countries), each *i*-th country’s research index is equal to the sum of clinical studies in the considered country (*K*_d, where *d*=1,…,m and m represents the total number of studies implemented in the analyzed sample):

\[
RESEARCH\_INDEX_i = \left[ \sum_{d=1}^{m} K_d \left( \frac{\sum_{i=1}^{n} L_i / \sum_{g=1}^{G} L_g}{\sum_{d=1}^{m} \sum_{i=1}^{n} L_i / \sum_{g=1}^{G} L_g} \right) \right] (1)
\]

weighted to the relative frequency of country locations (*L*), which are the medical facilities where the clinical studies are performed. This index represents a good proxy of pharmaceutical investments in Europe and, therefore, countries’ competitiveness on the European market of human experimentation.\(^\text{11}\)

Independent variables are mainly those proposed by previous works on the European market of human experimentation (Ippoliti, 2011). In details, they are the following: *Euro adoption, Wealth Index, Population* of the countries and *Gross Enrolment Ratio (GER)* for secondary level.

\(^\text{11}\) 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). According to the proposed index, we have 4 national clinical studies with a weight equal to 0.142857. Note that this work is assuming that the sample of patients is shared equally among different locations. Obviously, this assumption is affected by data availability.
Data about countries’ population and wealth index are extracted from the database of the International Monetary Fund, whereas data about GER are collected from the UNESCO database. Euro is a dummy variable equal to 1 if the Euro is the national currency, and it should catch the main economic conditions of these countries, especially those of Eastern Europe and their path towards the European Union. Population is necessary to indicate the size of these countries, whereas GER is linked to the difficulties faced by medical researchers in the enrollment process (i.e. awareness of expected and unexpected adverse events). Finally, the wealth index is a proxy of the countries’ competitiveness on the market of human experimentation (i.e. physicians’ fee). In particular, the index is expressed in relation to the $n$ European countries’ average, equal to 100. The formula is as follows:

$$WEALTH_{INDEX_i} = \left[ \frac{\sum_{i=1}^{n} W_i^t}{n} \right]$$

where $W$ is the gross domestic product (GDP) based on purchasing-power-parity (PPP) per capita of the $i$-th country in year $t$, with $n$ equal to 33. The proposed index measures how fast people’s wealth increases in each country in comparison to the average of the considered countries. Making several assumptions on the localization of production processes, it also measures national competitiveness on the European market of labor.

However, the most interesting explanatory variable – the truly innovative feature of this work compared to previous empirical analyses – is the Law reform. This variable is a dummy, equal to 1 if the reform is applied, 0 otherwise. This variable suggests the impact of the Italian law reform on the clinical research funded by the Industry, taking the other 32 European countries as counterfactual and maintaining all other control variables constant.

Table 1 introduces descriptive statistics about the proposed variables used in the empirical analysis. In the next section, the main empirical analysis on the proposed data-set is presented, through both a log likelihood estimation model and an ordinary least squares estimation model.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Obs.</th>
<th>Mean</th>
<th>Std. Dev.</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Index</td>
<td>247</td>
<td>-1.356169</td>
<td>3.314754</td>
<td>-12.70107</td>
<td>4.50951</td>
</tr>
</tbody>
</table>

12 International Monetary Fund, World Economic Outlook Database, April 2010.
13 This is the main idea suggested by Ippoliti (2011): considering the testing phase as any other production process that can be localized where the labor cost (physicians’ fee) is more competitive, i.e. where the index is positive.
3.2 Results

The data-set, which is a strongly balanced panel, is analyzed with STATA. Two main analyses are performed: a Poisson regression model (using count dependent variables) and a multiple regression model (using continuous dependent variables). In both cases the models are cross-sectional time-series with fixed-effects option. Obviously, according to the proposed approach, appropriate tests to validate relative assumptions about the variables are performed, along with the residuals of each analysis. Moreover, considering independent variables, the pairwise correlation is tested with acceptable results.

Considering the specific kind of sample (i.e. European countries), the fixed effect option is applied in order to reflect countries’ heterogeneity.\(^\text{14}\) Moreover, to test the hypothesis of non-correlation between individual effects and dependent variables, Hausman's specification test is carried out.\(^\text{15}\)

\(^\text{14}\) 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…”, and “…data coming from a smaller complete data set, with relatively few panels, prefer the fixed-effects estimator…”. This paper assumes that the considered sample could be thought of as the whole sample of a given potential population (i.e. a population of patients with common technology level of national health care system, as well as their access to medical facilities).

\(^\text{15}\) The test shows, with 5 degrees of freedom and a chi-squared test equal to 51.19 (Research Index), 52.44 (Clinical studies) and 51.50 (Medical centers), that difference in coefficients is not systematic, the null hypothesis can be rejected (p-value >chi2 = 0.0000), and the fixed effect estimator is appropriate. See Green (2003).
Table 2 proposes the Poisson regression model. The first column considers the number of medical centers involved in the experimental activities, whereas the second column considers the number of innovative medical options. The Poisson regression model is traditionally considered as the basic count model by full maximum likelihood estimation. Obviously, the Poisson probability distribution function of the dependent variables is tested, with acceptable results, to validate the proposed approach. On the other hand, an appropriate test to validate the assumption of normality distribution of dependent variables is also performed.

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>(count variable)</th>
<th>(count variable)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Medical centers</td>
<td>Clinical studies</td>
</tr>
<tr>
<td>Euro</td>
<td>1.492***</td>
<td>1.456***</td>
</tr>
<tr>
<td></td>
<td>(0.0205)</td>
<td>(0.0484)</td>
</tr>
<tr>
<td>Population</td>
<td>26.36***</td>
<td>29.01***</td>
</tr>
<tr>
<td></td>
<td>(0.373)</td>
<td>(0.829)</td>
</tr>
<tr>
<td>Wealth Index</td>
<td>5.584***</td>
<td>7.121***</td>
</tr>
<tr>
<td></td>
<td>(0.119)</td>
<td>(0.241)</td>
</tr>
<tr>
<td>GER secondary level</td>
<td>-0.0114***</td>
<td>-0.0153***</td>
</tr>
<tr>
<td></td>
<td>(0.000621)</td>
<td>(0.00132)</td>
</tr>
<tr>
<td>Law reform</td>
<td>0.375***</td>
<td>0.538***</td>
</tr>
<tr>
<td></td>
<td>(0.0325)</td>
<td>(0.0773)</td>
</tr>
</tbody>
</table>

F statistic (p value>chi2)

| Wald chi2(5) | 12120.91 |
| Prob > chi2  | 0.0000   |

Observations 260 260
Number of Countries 33 33

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

Since the Poisson regression model is a non-linear model, we cannot apply a traditional goodness-of-fit test such as the R-squared one. We could apply the pseudo R-square but, in this model, we are applying the fixed option to catch the heterogeneity of the proposed sample and therefore we are not able to estimate the log-likelihood of the intercept-only model, as suggested by Hilbe (2011). However, the model can also be supported by the deviance goodness-of-fit test. Indeed, considering the resulting chi2 p-value equal to 0.0000, the models are considered well fitting.

In table 3, a cross sectional time-series regression model with fixed-effects option is proposed but, in this case, a continuous variable is considered. Moreover, the bootstrap option is applied with 200...
replacements. Obviously, both dependent and independent variables are plotted in order to justify the normality assumption with acceptable results.

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>Research index</th>
<th>Clinical studies</th>
<th>Medical centers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euro</td>
<td>1.301***</td>
<td>1.313***</td>
<td>1.287***</td>
</tr>
<tr>
<td></td>
<td>(0.248)</td>
<td>(0.180)</td>
<td>(0.195)</td>
</tr>
<tr>
<td>Population</td>
<td>20.14***</td>
<td>19.72***</td>
<td>18.75***</td>
</tr>
<tr>
<td></td>
<td>(6.573)</td>
<td>(3.758)</td>
<td>(4.991)</td>
</tr>
<tr>
<td>Wealth Index</td>
<td>11.36***</td>
<td>8.560***</td>
<td>8.978***</td>
</tr>
<tr>
<td></td>
<td>(1.238)</td>
<td>(0.749)</td>
<td>(0.926)</td>
</tr>
<tr>
<td>GER secondary level</td>
<td>-0.0222**</td>
<td>-0.0201***</td>
<td>-0.0194***</td>
</tr>
<tr>
<td></td>
<td>(0.00874)</td>
<td>(0.00539)</td>
<td>(0.00595)</td>
</tr>
<tr>
<td>Law Reform</td>
<td>1.093*</td>
<td>1.095*</td>
<td>0.988*</td>
</tr>
<tr>
<td></td>
<td>(0.580)</td>
<td>(0.595)</td>
<td>(0.530)</td>
</tr>
<tr>
<td>Constant</td>
<td>-139.3***</td>
<td>-120.5***</td>
<td>-117.0***</td>
</tr>
<tr>
<td></td>
<td>(32.07)</td>
<td>(18.16)</td>
<td>(24.15)</td>
</tr>
</tbody>
</table>

F statistic (p value>chi2)
Wald chi2(5) 114.91 223.65 177.10
Prob > chi2 0.0000 0.0000 0.0000

R-squared
Within 0.3731 0.5163 0.4582
Between 0.7773 0.7770 0.8011
Overall 0.6629 0.4765 0.5794

Observations 243 243 243
Number of countries 33 33 33

The percentage of variation in the data explained by the model (i.e. R-squared) is pretty good, especially taking the Between into consideration, i.e. differences among countries. Also in this case the deviance goodness-of-fit test is validated, so that, considering the resulting chi2 p-value equal to 0.0000, the models are well fitting.

What about the interpretation of the coefficients?

Even if the estimator changes (full maximum likelihood estimation in the first case and ordinary least squares in the second one), the results are common and they confirm what has been suggested by the abovementioned analyses. On the one hand, the adoption of the Euro has a positive impact on the dependent variables, as do the population and the proposed wealth index. On the other hand, the GER for secondary level has a negative impact on the dependent variable. However, the most interesting explanatory variable is the law reform.
According to the proposed analysis, the reform has been able to increase the pharmaceutical clinical research. Table 2 suggests, with high statistical significance, that a potential reduction of transaction costs might be able to increase the investments of pharmaceutical companies in the testing phase. Even if with lower statistical significance, Table 3 can support the same positive correlation. Moreover, both analyses suggest that the impact of this law reform is higher when considering the number of clinical studies rather than the number of medical centers.

These results are absolutely coherent with the nature of the reform but, considering the degree of these coefficients, it would be interesting to investigate if something else could have been done to significantly increase the number of medical facilities involved in the production process of the pharmaceutical industry. Therefore, the predictable question is the following: is this law a wasted opportunity to reform the Italian competitiveness on the European market of human experimentation? In other words, which might be the most relevant wasted actions of this reform? Paradoxically, the best answer to the question is another question: what would happen if the law abrogated the second authorization of an experimental treatment in a satellite center?

According to Legislative Decree no. 211 of 24/06/2003, the authorization process of an experimental protocol requires a double opinion: the opinion of the IRB competent for the coordination center (i.e. the single opinion) and the second opinion by which each competent IRB accepts or refuses the initial opinion for another medical center. The law reform has regulated the administrative procedure of this mechanism (i.e. harmonization process) but not the second opinion. This is the wasted opportunity to significantly increase the competitiveness of the system, since the required time for two opinions is, at least, twice that needed to obtain a single opinion. The next table supports empirically the negative effect of the second opinion on the competitiveness of the Italian system.

The proposed model is a Poisson regression model and it uses the same dataset of the previous analysis even though the sample is smaller, i.e. 29 countries instead of 33 (excluded countries are Turkey, Romania, Luxemburg and Macedonia, Former Yugoslav Republic of); the considered panel is also more limited, i.e. from 2004 to 2007. On the one hand, taking countries into consideration, this choice is affected by limited data availability on national protection system.

Table 4: Poisson regression model (cross-sectional time-series with random-effects option)
Italy, from 2004 to 2007

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>(1) Medical Centers</th>
<th>(2) Clinical studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euro</td>
<td>-0.274</td>
<td>-0.232</td>
</tr>
</tbody>
</table>
The data are extracted from the report of the European Forum for Good Clinical Practice (EFGCP) on *The Procedure for the Ethical Review of Protocols for Clinical Research Projects in Europe* (2007).\(^{17}\) According to the report, three countries from the considered sample have adopted what this paper describes as the second opinion: Italy, the Czech Republic and Switzerland.\(^ {18}\) On the other hand, the considered panel is affected by the fact that the second opinion has been applied in Italy with the above mentioned law in 2003. In other words, this law could be seen as the starting point of an organized national system in Italy.

The model suggests that the adoption of a second opinion can decrease the number of medical centers involved in the experimental activities since, according to the proposed theory, the costs to implement an exchange between companies and patients increases. The result is more consistent, and coherent, if we consider that it is significantly and relatively high only with medical centers. Indeed, the number of national clinical studies should not be affected by the second opinion but by national features that have already been analyzed in the previous sections. This could be considered the wasted opportunity of the law reform, especially when comparing the two coefficients, i.e. *Law*

\(^{17}\) According to Smith (2007) and Madhu (2007), this report presents invaluable information about the ethical review process across Europe thorough a systematic analysis of national interpretation (i.e. implementation into national legislation) of EU Directive 2001/20/EC (2001).

\(^{18}\) The EFGCP report suggests that in Switzerland “…the Lead Ethic Commission makes the ethical decision on the study and the secondary RECs can accept or refuse this decision or eventually add locally determined minor supplements…”; whereas in the Czech Republic “…single-site trial ethical review is done by the relevant Local ethics committee; multi-site clinical trial ethical review is done by an ethics committee for multi-site studies (MEC) (and also by each of the Local ECs)…”.
This wasted opportunity could have had a positive impact increasing the expected number of medical centers to 45, i.e. increasing competitiveness on the European market of human experimentation.

There is still one open issue. Is this wasted opportunity a casual choice or a conscious choice? The answer can help us to understand how an ideal protection system might be structured.

4. Italian IRB system

Taking 2007 into account, there are 271 Institutional Review Boards (IRB) in Italy. Table 4 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 5. 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>
<thead>
<tr>
<th>Region</th>
<th>Population/IRB</th>
<th>IRB</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umbria</td>
<td>878709</td>
<td>1</td>
<td>878709</td>
</tr>
<tr>
<td>Piedmont</td>
<td>625292</td>
<td>7</td>
<td>4377047</td>
</tr>
<tr>
<td>P.A. of Trento</td>
<td>510194</td>
<td>1</td>
<td>510194</td>
</tr>
<tr>
<td>Emilia Romagna</td>
<td>472170</td>
<td>9</td>
<td>4249533</td>
</tr>
<tr>
<td>Veneto</td>
<td>436632</td>
<td>11</td>
<td>4802947</td>
</tr>
<tr>
<td>Puglia</td>
<td>313324</td>
<td>13</td>
<td>4073208</td>
</tr>
<tr>
<td>Toscana</td>
<td>281356</td>
<td>13</td>
<td>3657630</td>
</tr>
<tr>
<td>P.A. of Bolzano</td>
<td>245396</td>
<td>2</td>
<td>490792</td>
</tr>
<tr>
<td>Campania</td>
<td>232032</td>
<td>25</td>
<td>5800789</td>
</tr>
<tr>
<td>Abruzzi</td>
<td>219482</td>
<td>6</td>
<td>1316892</td>
</tr>
</tbody>
</table>
Table 6 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), whereas data about the dependent variables are the same as those of the previous analysis. 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 proposed 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 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 5 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.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number of IRB</th>
<th>Number of IRB</th>
<th>Number of IRB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy</td>
<td>219097</td>
<td>271</td>
<td>59375295</td>
</tr>
<tr>
<td>Marche</td>
<td>171620</td>
<td>9</td>
<td>1544581</td>
</tr>
<tr>
<td>Lazio</td>
<td>167490</td>
<td>33</td>
<td>5527163</td>
</tr>
<tr>
<td>Sardinia</td>
<td>166253</td>
<td>10</td>
<td>1662530</td>
</tr>
<tr>
<td>Liguria</td>
<td>160885</td>
<td>10</td>
<td>1608850</td>
</tr>
<tr>
<td>Molise</td>
<td>160228</td>
<td>2</td>
<td>320456</td>
</tr>
<tr>
<td>Lombardy</td>
<td>157277</td>
<td>61</td>
<td>9593924</td>
</tr>
<tr>
<td>Sicilia</td>
<td>156977</td>
<td>32</td>
<td>5023272</td>
</tr>
<tr>
<td>Calabria</td>
<td>154068</td>
<td>13</td>
<td>2002880</td>
</tr>
<tr>
<td>Friuli Venetia Giulia</td>
<td>152167</td>
<td>8</td>
<td>1217332</td>
</tr>
<tr>
<td>Basilicata</td>
<td>147793</td>
<td>4</td>
<td>591170</td>
</tr>
<tr>
<td>Valle d'Aosta</td>
<td>125396</td>
<td>1</td>
<td>125396</td>
</tr>
</tbody>
</table>

Sources: AIFA and ISTAT

Table 6: Poisson regression model (cross-sectional time-series with fixed-effects option)
Italy, from 2000 to 2007

19 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/](http://www.agenziafarmaco.gov.it/).
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.

5. 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).

<table>
<thead>
<tr>
<th>variable</th>
<th>coefficient</th>
<th>p-value</th>
<th>Std. error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical centers</td>
<td>0.109***</td>
<td>0.0360</td>
<td></td>
</tr>
<tr>
<td>Clinical studies</td>
<td>0.0873***</td>
<td>0.0276</td>
<td></td>
</tr>
<tr>
<td>Research Index</td>
<td>0.0961***</td>
<td>0.0311</td>
<td></td>
</tr>
<tr>
<td>Law reform</td>
<td>-0.151**</td>
<td>0.0709</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-0.148**</td>
<td>0.0700</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-0.130*</td>
<td>0.0682</td>
<td></td>
</tr>
</tbody>
</table>

F statistic (p value>chi2)

<table>
<thead>
<tr>
<th></th>
<th>Wald chi2(2)</th>
<th>Prob &gt; chi2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10.17</td>
<td>0.0062</td>
</tr>
<tr>
<td></td>
<td>10.98</td>
<td>0.0041</td>
</tr>
<tr>
<td></td>
<td>10.52</td>
<td>0.0052</td>
</tr>
</tbody>
</table>

Observations: 8
Number of Countries: 1

Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
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 reduce 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 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 empirical analysis’ results. What about the second opinion?

The empirical results suggest that the Italian law reform has managed to increase the country’s competitiveness. The harmonization process of the administrative procedures needed to obtain opinions on clinical trials can facilitate pharmaceutical companies in the authorization process since, before this law reform, each IRB used to adopt whichever administrative process they wanted (e.g. applications, models and required documents). Each medical center meant a different administrative procedure and thus an increase in the expected transaction costs. Harmonizing the procedures can certainly reduce the required time. However, the empirical results suggest that the absence of any changes in the procedure to obtain the authorization for a satellite center has been a wasted opportunity. Without the second opinion the time needed to start operating in all selected satellite centers might be significantly lower, therefore boosting the competitiveness of the Italian centers on the European market of human experimentation. Based on our normative analysis, the second opinion should be avoided since it represents an obstacle to the exchange. But, is it an unknown wasted opportunity or a conscious choice?

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.\textsuperscript{20} Obviously, the members’ 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

\textsuperscript{20} According to the 5\textsuperscript{th} 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.
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.

There is a final issue: what about the risk of collusion? Is socially acceptable the risk of collusion between competitive IRBs and pharmaceutical companies due to the competitiveness?

A competition can be an incentive to collude. In other words, the necessity to work faster than others, as well as the necessity to survive on pharmaceutical companies’ fee, might be an incentive to collude with industry, forgetting the real target of an IRB. The competition might achieve the target but missing the point. Obviously, the public stakeholder should consider the consequence of these opportunities. In other words, the public policy should be shaped considering both the opportunity to minimize the required time to review a trial and some legal tools to prevent collusion between IRBs and pharmaceutical companies.

However, besides the positive analysis in the empirical section, there are some weaknesses that can affect the achieved results. The main weakness is related to the considered sample and to the statistical assumption about extraction from an hypothetical population of companies (NIH dataset), which is affected by data availability. Studies on a more complete dataset, if it becomes available, will be an opportunity to strengthen the achieved results and to increase the current knowledge. Further developments might concern empirical works with more countries to better analyze the impact of IRBs on pharmaceutical clinical research. However, this approach could be affected by data availability and the need for homogeneous data about clinical research and explanatory variables. Finally, further developments might concern the compatibility between a public policy aimed to minimize the required time to review a trial and the goodness of that review (i.e. research subjects’ safety).
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