Trials, Tricks and Transparency: How Disclosure Rules Affect Clinical Knowledge*

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Abstract

Scandals of selective reporting of clinical trial results by pharmaceutical firms have underlined the need for more transparency in clinical trials. We provide a theoretical framework which reproduces incentives for selective reporting and yields three key implications concerning regulation. First, a compulsory clinical trial registry complemented through a voluntary clinical trial results database can implement full transparency (the existence of all trials as well as their results is known). Second, full transparency comes at a price. It has a deterrence effect on the incentives to conduct clinical trials, as it reduces the firms' gains from trials. Third, in principle, a voluntary clinical trial results database without a compulsory registry is a superior regulatory tool; but we provide some qualified support for additional compulsory registries when medical decision-makers cannot anticipate correctly the drug companies' decisions whether to conduct trials.

Keywords: pharmaceutical firms, strategic information transmission, incentives, clinical trials, registries, results databases, scientific knowledge

JEL classification: D72, I18, L15

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1 Introduction

May 20, 2005, saw the first ever international clinical trials day, underlining the importance of clinical trials to medical research.[1] Since they provide the most reliable way to test the efficacy and safety of medical treatments, randomized controlled clinical trials constitute one of the main tools of scientific medicine. Without trials, ineffective treatments or, even worse, harmful interventions may be accepted in medical practice. Accordingly, the appropriate design of the incentives to conduct clinical research is considered to be of enormous importance as the following quote from the medical literature shows: "*Randomised trials conducted over the past half century have helped to bring about a situation in which health care has been credited with three of the seven years of increased life expectancy over that time and an average of five additional years of partial or complete relief from the poor quality of life associated with chronic disease*" (Chalmers (1998)).

Recently, however, there have been a number of highly publicized cases in which pharmaceutical firms have selectively disclosed evidence on marketed drugs (see e.g. Curfman et al. (2005), Harris and Koli (2005), Avorn (2006), Harris (2007), or Berenson (2007)).[2] These scandals have generated a controversial debate about the appropriate design of a vigorous research enterprise that brings innovations to patients as quickly as possible. The consent that the parties associated in clinical trials–patients, doctors, researchers, medical journal editors, pharmaceutical industry, funders and government–have reached is that greater transparency in clinical trials is needed.[3] To achieve this transparency there are mainly two policy proposals discussed: clinical trial registries and clinical trial results databases.[4]

A *clinical trial registry* contains information on ongoing clinical studies. As a result of the growing

[1] Since 2005 the international clinical trials day has been celebrated yearly on or near the 20th of May. The event is promoted by the European Clinical Research Infrastructures Network.

[2] The problem of selective publication of clinical trial results has already been recognized long ago and almost twenty years ago the first voices were raised demanding to require registration of all clinical trials prior to initiation (Simes (1986)).

[3] The medical literature discusses a second source of selective reporting. This is the so-called publication bias. It refers to the fact that for peer-reviewed journals negative and inconclusive trials are much less interesting than positive trials. Consequently, they are less likely to be published (See e.g. De Angelis et al. (2004)).

[4] Another measure discussed to solve the problem of selective reporting are reporting requirements about a sponsor's role in clinical studies. Starting point is the so-called problem of conflict of interest. As a result of an increase in the costs of clinical trials the pharmaceutical industry has increased its influence on the design, conduct and result reporting of clinical trials (for example through so-called contract research organizations). If the firm's influence is very strong, then "the results of the finished trial may be buried rather than published if they are unfavorable to the sponsor's product" (Davidoff (2001), p. 825). See e.g. Krimsky (1999), Sismondo (2008), and the references in Davidoff (2001) for evidence about the existence of this problem. The present paper makes the benchmark assumption that the firm's interests completely determine results reporting.

support for registries, several voluntary registries have been created by, for example, public health authorities and the pharmaceutical industry.[5] However, given the limited success of these voluntary registries in solving the problem of selective reporting of clinical trials, policy proposals promote now the idea of a compulsory registry of all clinical trials. Recently, the International Committee of Medical Journal Editors promoted a compulsory registry by requiring registration of clinical trials as a condition of their subsequent consideration for publication.[6] This effort is complemented by the definition of a minimum trial registration dataset by the World Health Organization aimed at standardizing the way information is made available to the public (see e.g. Gulmezoglu et al. (2005)). There are attempts to create additional incentives for registering by, for example, urging institutional review boards (of e.g. universities or hospitals) to consider registration of clinical trials a condition for approval. Also, around the world, governments are beginning to legislate mandatory disclosure of all trials. Thus, there is a tendency to create a de facto compulsory registry of clinical trials.

A *clinical trial results database* contains (a summary of) the results of completed clinical studies, regardless of outcome. As a result of the scandals caused through selective publication of trial results even the pharmaceutical industry acknowledges that there is a problem and (at least a part of) the pharmaceutical industry is supporting the creation of results databases.[7] Databases are often proposed in combination with a compulsory trial registry. For example, on September 27, 2007, President Bush signed into law The Food and Drug Administration Revitalization Act, which contains mandatory registration and results reporting requirements (Drazen (2007)).[8]

[5] See the account in Horton and Smith (1999).

[6] The disclosure refers to public registration of summary protocols at the initiation of all trials whose primary purpose is to affect clinical practice (phase III trials). Trials to assess major unknown toxicity or determine pharmacokinetics (phase I trials) are excluded. Trials between these two extremes (phase II trials) are decided on a case-by-case basis, see De Angelis et al. (2004 and 2005).

[7] The European Federation of Pharmaceutical Industries and Associations (EFPIA), the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the Japanese Pharmaceutical Manufacturers Association (JPMA) and the Pharmaceutical Research and Manufacturers of America (PhRMA) released on January 6, 2005, a "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases" (available at http://129.35.73.130/wps/PA_1_0_J0/FINAL%20Position %20Clinical%20Trials%20Information%20January%2005.pdf, accessed on January 4, 2008). In this document the industry commits to register ongoing trials (other than exploratory) and to disclose results, regardless of outcome. In a similar vein is the statement of the Biotechnology Industry Organization (available at http://www.bio.org/bioethics/background/20050621.asp, accessed on January 4, 2008). In addition, for example, GlaxoSmithKline has created a results database and commits to disclose trial summaries "whether or not the data may be judged as positive or negative for its products" (Rockhold and Krall (2006)).

[8] The signing into law of this act does not imply that the discussion about the design of regulation is settled. On the one hand, in the U.S. the act must be followed by rule making and the environment in which clinical trials take place is mainly shaped by other legislation. The U.S. Congress, for instance, is currently considering The Fair Access to

This paper aims at contributing to the debate about the appropriate design of the incentives to conduct medical research by providing a formal analysis of clinical trial registries and research databases. Given that the scandals mentioned before have been caused by selective reporting of evidence on marketed drugs, the main focus of the present paper is on postmarketing studies.[9] This is the fastest-growing area of clinical research today. One reason for this is that trials before access to the market leave residual but important uncertainty. This uncertainty is accepted at the time of distribution and once the drug is in the market it is agreed that potential adverse events should be monitored through postmarketing clinical trials (Pouvourville (2006)).[10] Notice that not all postmarketing studies are required by the FDA at the time of approval of a new drug (see Glasser et al. (2007)).[11] For instance, postmarketing studies are also conducted upon approval of a new drug in order to study the compound for potential use for other medical conditions.

In a nutshell, our analysis starts from the fact that clinical trials constitute an investment in information by pharmaceutical firms. Registries and databases affect the return on this investment by restricting the way in which drug companies transmit knowledge to medical decision-makers. They are, therefore, likely to affect the firm's investment in information, that is, the decision whether or not to conduct clinical trials.

From a strategic point of view–once a clinical trial has been carried out–the scope of pharmaceutical firms is limited. Firms can hold back information about unfavorable trials but they cannot lie and forge the entire evidence in a clinical trial in their favour.[12] Holding back trial results considered 'negative'

Clinical Trials Act which is an amendment to the Public Health Service Act. On the other hand, in other parts of the world similar rules are discussed. For instance, several European countries have established disclosure rules in the form of registries or results databases, while others are discussing such rules.

[9] To the extent that the monotonicity assumption (which we state below) holds for the relevant parameter range, our analysis also applies to approval trials for new drugs and to approval trials for new indications of already existing drugs.

[10] At an annual growth rate of 23%, industry investment in postmarketing research is expected to top $12 billion in 2007 (Research and Markets (2007)). According to a study from the Tufts Center for the Study of Drug Development, between 1998 and 2003 the FDA requested postmarketing commitment studies in 73% of the approvals for new drugs (Tufts CSDD (2004)). Other incentives to conduct postmarketing studies may come from the widespread adoption of drug formularies. Pharmaceutical firms face strong pressure to provide clinical and economic data that justify their inclusion in the formulary (Folland et al. (2004)).

[11] The so-called postmarketing commitments (PMC) are negotiated with the sponsor. Concerning these trials our model would predict that registries and databases affect the bargaining position of the sponsor. Moreover, the firm retains the power to design the trial and to determine whether the safety of a drug is fully explored (Vlahakes (2006)). Postmarketing study designs include also designs different from clinical trials. Given the simple model of clinical trials in the present paper, we believe that it can also be applied to much of this postmarketing research.

[12] While we assume that pharmaceutical firms cannot forge the entire evidence in a clinical trial, we acknowledge that there is evidence that the results of a trial might be manipulated. For instance, results might be presented in such a form that the trial appears to be more positive than it really is (see e.g. Chan et al (2004). See also Dickersin (2008) for an extensive review of the problems associated to the reporting of trial results. We are grateful to a referee for pointing

is the so-called problem of selective disclosure of trial results which has generated the debate about reform. Despite the difficulty in quantifying the impact of selective reporting due to the lack of data from unpublished trials, the existing evidence suggests that it is, indeed, a relevant problem.[13]

We propose a game of hard evidence (Milgrom (1981)) as the appropriate model of clinical trials and information transmission from pharmaceutical firms to the public. Inspired by the recent political economy literature on strategic information transmission by interest groups (see Bennedsen and Feldmann (2006) or Dahm and Porteiro (2008)), we propose a two stage game in which firms choose in the first stage whether or not to conduct clinical trials. The publication of clinical trial results affects product market competition in the second stage. We model the second stage through a very mild monotonicity assumption saying that it is advantageous for pharmaceutical firms to publish clinical trial results showing that their products are more effective or have fewer side-effects than thought (this assumption is not only natural, but also in line with the existing evidence in, for instance, the antiulcer-drug market; see Azoulay (2002)).

Our model predicts that in the benchmark without disclosure requirements (we call this the laissez-faire scenario) firms conform to the behavior that triggered the before mentioned scandals and report their trial results selectively. We analyze then successively the main policy proposals discussed. We study first voluntary registries and find that they offer no advantage to pharmaceutical firms. Hence, our approach predicts that these registries will not be used and explains why voluntary registries could not solve the problem of selective reporting of trial results. We turn then to the effects of a compulsory registry of clinical trials. We show that a compulsory registry has a deterrence effect that reduces the incentives of pharmaceutical firms to conduct trials and cannot solve the problem of selective reporting. When a compulsory registry is complemented through a clinical trials results database we show that a regime of 'full transparency', in which the decision-maker knows about the existence of all trials as well as their results, can be implemented. A key result of our paper, however, concerns the

this out to us. However, since clinical trial registries and results databases have been promoted to deal with selective reporting, we sidestep this issue here.

[13] Turner et al. (2008), have analyzed this issue for the market of antidepressants by comparing evidence obtained from reviews of the FDA about registered trials, with published reports. They find a substantial bias in publication: while 36 out of 37 trials viewed as positive by the FDA were published, this is true for only 3 out of 36 of those viewed as negative (or questionable). Also, in a recent paper, Rising et al. (2008) find a substantial bias in publication by analizing efficacy trials submitted to the Food and Drug Administration (FDA) in approved New Drug Applications (NDAs) and comparing the trial characteristics as reported by the FDA with those reported in publications. They find that 78% of the efficacy trials in the NDAs were published; trials with favorable outcomes were nearly five times as likely to be published as those without favorable outcomes. Moreover, nearly half (47%) of the 43 primary outcomes reported in the NDAs that showed no statistically significant benefit for the tested drug were not included in the papers. See also Chan et al. (2004).

potential adverse effects of 'full transparency' in clinical trials. We show that an important trade-off emerges. As 'full transparency' reduces the firm's gains from clinical trials, fewer trials are conducted. Obtaining more precise information about the trials conducted comes at the expense of deterring some trials.

The policy implications of the present paper depend crucially on the degree of sophistication of medical decision-makers or, more precisely, on their capacity to draw accurate inferences about the pharmaceutical firms' incentives to perform clinical trials. If decision-makers possess the information necessary to devise a fully sophisticated skeptical strategy, then the best policy is, unambiguously, that of promoting the use of voluntary results databases, without the need of a registry. This policy alternative allows the decision-makers to extract all the information that the firms acquire through the trials and, at the same time, increases the pharmaceutical firms' incentives to undertake clinical trials compared with the laissez-faire scenario. As in Milgrom and Roberts (1986) a skeptical strategy is a powerful information acquisition tool: (i) In combination with a database it solves the problem of selective reporting because decision-makers think that, if a drug company does not post results in a database, this is because it conducted a negative trial. The firm in turn wants to avoid this impression and uses the database to prove that a trial was inconclusive or positive. (ii) Moreover, incentives to conduct trials are stimulated because a company expected to conduct trials that fails to post results in databases is believed to have conducted a negative trial. Since this is the worst impression the firm can give, not conducting a trial is very expensive. In other words, such a policy reduces the opportunity costs of conducting trials.

When decision-makers are unsophisticated (because they lack the information required to draw precise inferences) there is no clear-cut recommendation to be made. The two alternative policies that are candidates to being optimal are laissez-faire and a compulsory registry complemented through a database. Which regime is optimal depends on how society values more trials (in laissez-faire) versus more precise information (with the intervention). We offer a deeper analysis of this trade-off and provide some qualified support for the latter. The reason is that the information gained relates to drugs society knows less about.

The structure of the paper is as follows. The next section presents our model of clinical trials. Section 3 analyzes the laissez-faire scenario without policy, while Section 4 studies the implications of registries and results databases. Section 5 relaxes the assumptions concerning the information the decision-maker possesses and her degree of sophistication when drawing inference from it. The last section offers some concluding remarks.

2 A Model of Clinical Trials

We consider a pharmaceutical firm that produces a drug for a particular therapeutic market. Success in product market competition depends on the perceived 'quality' q of the company's product in the eyes of market participants. This perceived 'quality' refers to gross effectiveness and how this effectiveness is diminished as a result of side-effects, contraindications, interactions with other treatments, and the like.

Prior to the outcome of product market competition the firm can conduct a clinical trial in order to improve the position of the firm's product in the market by improving the perceived 'quality' q. For our model it does not matter whether we think of this trial as superiority, non-inferiority or equivalence trial and whether the point of comparison is an established therapy or a placebo. In all those cases a successful trial has the potential to increase the perceived 'quality' of the firm's product. However, in order to fix ideas we find it convenient to illustrate our model with the example of a firm designing a trial to show that its product is not worse than its competitors'.

A clinical trial can have three possible outcomes. First, the trial can show the equivalence of two approaches of treatment. We will refer to this outcome as a positive trial. Second, the trial can show that the firm's product is inferior, a situation to which we will refer as negative trial. Third, the trial can be inconclusive (see De Angelis et al. (2004)).

We model clinical trials as follows. There are two states of the world $\{0, 1\}$ and we denote the true state of the world by ω. The interpretation is that in state 0, the firms drug is inferior, while in state 1 both treatments are equivalent. Initially, the probability that the firm's drug is equivalent is $q > 0$. Thus, the perceived 'quality' q measures quality in the sense that it answers the question how likely it is that the firm's product lives up to its expectations.

The firm can conduct a clinical trial at a cost $K > 0$. The result of the clinical trial is denoted by t. The clinical trial reveals with probability $x \in [0, 1]$ the true state of the world, that is, $t = \omega$. With probability $1 - x$, the trial is inconclusive, that is, $t = \emptyset$. The information revealed through a trial is hard evidence. This captures the fact that a pharmaceutical firm cannot forge the entire evidence of clinical trials indicating that certain desirable treatment effects exist when they do not. However, the scandals mentioned in the Introduction indicate that the firm can selectively report trial results. We denote the firm's report or message by M. If the trial reveals that the firm's drug has serious side-effects and is not equivalent to the competitors', that is $t = 0$, then the firm can hide this trial. Thus, if $t = \omega$, the pharmaceutical firm can decide to publish the result of the test or not, i.e., $M \in \{\omega, \emptyset\}$. If the trial is inconclusive, that is, $t = \emptyset$, then the pharmaceutical firm can not forge evidence and has to report this fact, that is, $M = \emptyset$. Although in reality there are many different medical decision-makers who use clinical trial results, for simplicity we postulate that there is just one

representative medical decision-maker who receives the message.

To make the analysis interesting, unless otherwise stated, we focus on situations in which the perceived 'quality' of the firm is not maximal ($q < 1$) and trials can be successful ($x > 0$). The precise timing of this game is as follows:

Stage 1: The firm decides whether to conduct a clinical trial.

Stage 2: A message M is sent to the medical decision-maker (if no trial has been conducted, $M = \emptyset$).

Stage 3: The medical decision-maker updates her belief about the perceived 'quality' of the firm's product to q_x.

Stage 4: Product market competition takes place.

This game is solved by backward induction. However, instead of solving one specific model for stage 4, we assume, in principle, any model in which the firm has an incentive to generate scientific knowledge:

Monotonicity Assumption: The equilibrium profits of the firm resulting from product market competition, denoted by $E\Pi(q)$, are strictly increasing in its perceived 'quality' q.

We argue now that this assumption is very mild. First, given that we aim at looking at how incentives to conduct clinical trials are affected through registries, supposing that profits depend on trial outcomes is the conservative assumption to make. Starting with a situation in which there are no incentives to conduct trials would obscure the picture. Second, increasingness of firms' profits on perceived quality is in line with the few existing empirical evidence available which comes from the antiulcer-drug market (Azoulay (2002)).[14]

Finally, as we will see throughout the paper, an important element for the analysis will be the extent to which the market rewards a higher perceived 'quality'. The monotonicity assumption only requires that firms' profits are increasing in the quality, but does not impose any restriction on the shape of the profit function $E\Pi(q)$. For the sake of future reference we will say that the pharmaceutical firm enjoys *increasing returns to quality* whenever the marginal impact of an increase in the perceived 'quality' is increasing in q (i.e., if the profit function is increasing and convex in q). Conversely, we will say that the firm faces *decreasing returns to quality* if the marginal effect of an increase in the perceived 'quality' is decreasing (i.e., if the profit function is increasing and concave in q).

[14] The function $E\Pi(q)$ that summarizes the outcome of product market competition has been kept sufficiently general so as to encompass different possibilities depending on the interpretation of our model. In particular, one can construct microfoundations for the profit function $E\Pi(q)$ based on models of detailing (building on the seminal work on promotional advertising by Schmalensee (1976)) or, alternatively, based on a model of informative advertising in the line of Brekke and Kuhn (2006). The details of these two applications of our model are available upon request.

3 The Benchmark Scenario: Laissez-faire

"The pharmaceutical industry has systematically misled physicians and patients by suppressing information on their drugs..."

Representative Henry Waxman (D-CA) at a hearing (Couzin (2004a)).

We study now the benchmark scenario for clinical trials, in which firms are completely unconstrained in their decision whether to conduct trials. We show that this leads to selective reporting.

Under laissez-faire, the medical decision-maker does not observe the pharmaceutical firm's decision whether to invest in clinical tests or not. As a result, she has to base her behavior on her beliefs about what the firm is doing. The appropriate equilibrium concept is, hence, a Perfect Bayesian Equilibrium (PBE) in which both the decision-maker and the pharmaceutical firm behave optimally, given their beliefs about the other's action and these beliefs are, at equilibrium, correct. As usually, there might be multiple equilibria and we search first for a PBE in which clinical trials are conducted.

Notice first that, given that clinical trial results are hard evidence, if the firm reports low quality ($t = 0$), then the decision-maker infers $q_x = 0$. Because of the monotonicity assumption, this message strategy is not a best reply. Consequently, the pharmaceutical firm only discloses information that favors its cause. Damaging evidence is hidden. Formally, selective reporting is as follows

$$M = \begin{cases} 1 & \text{if } t = 1 \\ \emptyset & \text{if } t \in \{0, \emptyset\} \end{cases}. \tag{1}$$

A decision-maker expecting trials to take place updates beliefs as follows

$$q_x = \begin{cases} \Pr(w = 1 | M = 1) = 1 & \text{if } M = 1 \\ \Pr(w = 1 | M = 0) = 0 & \text{if } M = 0 \\ \Pr(w = 1 | M = \emptyset) = \frac{\Pr(M=\emptyset | w=1) \Pr(w=1)}{\Pr(M=\emptyset)} = \frac{q(1-x)}{1-xq} < q & \text{if } M = \emptyset \end{cases}. \tag{2}$$

That is to say, if the decision-maker receives no evidence, taking into account selective reporting, she expects that it is more likely that the product is of low quality (the true state is 0), since the pharmaceutical firm may have received this information and decided not to disclose it (a negative trial was conducted).

Given this, the expected profits of the firm from investing in a clinical trial are

$$E\Pi_t = xqE\Pi(q_x = 1) + (1 - xq) E\Pi\left(q_x = \frac{q(1-x)}{1-xq}\right) - K. \tag{3}$$

With probability xq there will be a positive trial and the beliefs of the decision maker will be $q_x = 1$. However, in the remaining cases the trial will be negative or inconclusive and the perceived 'quality'

diminishes to $q_x = q(1-x)/(1-xq)$. Profits when the firm does not invest in a trial are

$$E\Pi_{No\_t} = E\Pi\left(q_x = \frac{q(1-x)}{1-xq}\right). \tag{4}$$

The reason is that the firm is expected to invest and lack of positive trial results deteriorates the firm's position in the market. The pharmaceutical firm invests in the trial if and only if

$$E\Pi_t - E\Pi_{No\_t} > 0 \Leftrightarrow K < \mathbb{K}_t^{LF} \equiv xq\left(E\Pi\left(q_x = 1\right) - E\Pi\left(q_x = \frac{q(1-x)}{1-xq}\right)\right).$$

Provided the above inequality holds, this corresponds to a PBE. We summarize this in the following result:

Proposition 1 *Under laissez-faire, there exists a PBE in which the pharmaceutical firm performs a clinical trial provided trials are cheap enough, that is,* $K \leq \mathbb{K}_t^{LF}$.

So we have seen that in a world without regulation, there will be clinical trials. We will now check when there exists a PBE in which the firm is correctly expected not to perform trials.

If a trial is conducted, reporting is selectively as before, formalized in (1). However, if the decision-maker does not expect the firm to invest in a trial, then she will update her beliefs differently from (2)

$$q_x = \begin{cases} 1 & \text{if } M = 1 \\ 0 & \text{if } M = 0 \\ q & \text{if } M = \emptyset \end{cases}. \tag{5}$$

That is to say, if no evidence is received, she will consider that no trial has been conducted and she will not update her beliefs. Expected profits from a trial are

$$E\Pi_t = xqE\Pi\left(q_x = 1\right) + \left(1 - xq\right)E\Pi\left(q_x = q\right) - K, \tag{6}$$

and those from not performing the trial become

$$E\Pi_{No\_t} = E\Pi\left(q_x = q\right). \tag{7}$$

The pharmaceutical firm will not invest in the trial if and only if

$$E\Pi_t - E\Pi_{No\_t} < 0 \Leftrightarrow K > \mathbb{K}_{No\_t}^{LF} \equiv xq\left(E\Pi\left(q_x = 1\right) - E\Pi\left(q_x = q\right)\right).$$

Proposition 2 *Under laissez-faire, there exists a PBE in which the pharmaceutical firm does not perform a clinical trial provided trials are expensive enough, that is,* $K \geq \mathbb{K}_{No\_t}^{LF}$.

It is straightforward to check that $\mathbb{K}_t^{LF} \geq \mathbb{K}_{No\_t}^{LF} > 0$, implying that for $K \in \left[\mathbb{K}_{No\_t}^{LF}, \mathbb{K}_t^{LF}\right]$ the two equilibria coexist and the beliefs of the decision-maker determine whether we have equilibrium with or without clinical trials. It will prove useful to underline at this point that when there exists no regulation the decision whether or not to invest in trials depends only on the costs of trials and the degree to which, following the monotonicity assumption, the firm's profits increase in its 'perceived' quality. For later reference we summarize this as follows.

Corollary 1 *Under laissez-faire, if trials are cheap enough in the unique PBE clinical trials are performed–independently of the conditions under which product market competition takes place.*

The situation described in this subsection has shown how, in the absence of any policy, the performance of clinical trials is characterized by (i) a lack of observability of the trials that are actually performed and (ii) selective reporting of the test result by firms. These are the main reasons that have led to a demand for regulation. The analysis of the policies proposed is the subject of our concern in the next section.

4 Policies

> *"Honest reporting begins with revealing the existence of all clinical studies, even those that reflect unfavorably on a research sponsor's product. ... We are far from this ideal at present ..."*
>
> De Angelis et al. (2004, p. 477).

As the previous section has emphasized, in the absence of any policy there is a serious lack of transparency concerning clinical trials that affects both the observability of the trials that are performed, and the disclosure of the test results. Consequently, policy proposals have been formulated in order to achieve "*full transparency with respect to performance and reporting of clinical trials*" (De Angelis et al. (2004), p. 477). Before analyzing in detail the implications of these policies, let us define, more precisely, what we will consider as "full transparency" throughout the paper.

Definition 1 *A policy implements a regime of full transparency if the decision-maker can observe which trials are conducted and knows all the results obtained through the trials.*

In what follows we analyze successively the main policies proposed. The premise for our analysis is that policymakers aim at minimizing the uncertainty about the efficacy and the therapeutic advances of new drugs. However, notice that this uncertainty is not only reduced when more is learned from

a given clinical trial. It is also reduced when more trials are carried out. Therefore, throughout the paper, we will consider policies as more appealing, the more they stimulate honest reporting (i.e., transparency) and the performance of clinical trials.[15]

4.1 Voluntary Registries of Clinical Trials

> *"...the Pharmaceutical Research and Manufacturers of America (PhRMA), a Washington D.C.–based trade group, says it would prefer for Congress to wait and "see if the voluntary efforts are going to work," says spokesperson Jeff Trewitt."*
>
> Couzin (2005).

In order to improve transparency in clinical trials voluntary clinical trial registries have been created. A clinical trial registry contains information about ongoing clinical studies. As a result, a trial's existence is part of the public record and this knowledge can be used for medical decision making. Can voluntary clinical trials registries improve the situation with respect to the laissez-faire?

First, notice that, although voluntary clinical trials registries exist, there is always the possibility that the firm makes no use of the voluntary registry and that the decision-maker does not take it into account for her belief formation. This implies that the two equilibria presented in Propositions 1 and 2 still exist.

Second, can there be a PBE in which the decision-maker correctly expects the firm to conduct only trials that have previously been registered in a voluntary registry? Suppose the decision-maker expects the firm to conduct only trials that have previously been registered in a voluntary registry. If a trial is conducted, reporting is selectively as before, formalized in (1). If the firm registers but does not provide evidence from positive trials, the decision-maker infers that a trial has been conducted and updates beliefs as in (2). Expected payoffs are given by (3). However, assume the firm avoids registering although a trial is conducted. In case that it does not provide evidence from positive trials, the decision-maker infers that no trial has been conducted and updates beliefs as in (5). Hence, the firm's profits are given by (6). Thus, the firm has no incentive to register the trial.

Proposition 3 *Voluntary clinical trial registries have no effect. In particular, there does not exist a PBE in which the firm conducts only trials that have previously been registered.*

[15] At this point it is worth mentioning the recent controversy about the lack of real therapeutic advances in most of the new drugs that appear in the market (see Prescrire International 2007). We believe that, even in those cases, transparent clinical trials that provide an assessment of the real therapeutic gains of the new drugs, are a valuable tool for decision-makers.

The fact that voluntary registries could not solve the problem of selective reporting has been the starting point for the demand for more intervention in clinical trials (see De Angelis et al. (2004)). We analyze now compulsory registries.

4.2 Compulsory Registries of Clinical Trials

> *"One solution, some in Congress say, is a mandatory registry, in which all clinical trials must be registered at their inception"*
>
> Couzin (2004b).

With a compulsory registry in place the pharmaceutical firm cannot publish (disclose) evidence from a trial not registered in advance. The whole point of a registry is that, if the firm decides to invest in a trial, this decision becomes observable for the public. As a result, the behavior of the decision-maker is no longer based on her beliefs about what the firm is doing. The firm selectively reports as in (1), the decision-maker updates beliefs as in (2) when she observes investment in trials in the registry, and expected profits from conducting a trial become those in (3). However, if no investment in a trial is made by the firm, this is reflected in the registry. Thus, the decision-maker does not update beliefs and the firm's profits from not investing in the trial are given by (7). The pharmaceutical firm invests in the trial if and only if the former is larger than the latter which is the same as

$$K < xqE\Pi\left(q_x = 1\right) + (1 - xq)E\Pi\left(q_x = \frac{q(1-x)}{1-xq}\right) - E\Pi\left(q_x = q\right) \tag{8}$$

$$\Leftrightarrow K < \mathbb{K}^{CR} \equiv xq\left[E\Pi\left(q_x = 1\right) - E\Pi\left(q_x = q\right)\right] - (1 - xq)\left[E\Pi\left(q_x = q\right) - E\Pi\left(q_x = \frac{q(1-x)}{1-xq}\right)\right].$$

Summarizing, we have that the following holds.

Proposition 4 *In the unique PBE with a compulsory clinical trial registry, the pharmaceutical firm conducts a clinical trial if trials are cheap enough, that is, $K \leq \mathbb{K}^{CR}$; and decides not to generate scientific knowledge otherwise.*

This result says that when trials are cheap enough, a compulsory clinical trial registry can solve part of the problem: medical decisions are taken based on all trials conducted. However, the problem of selective reporting is still there. In addition, incentives for investment in trials are reduced. This is so because $\mathbb{K}^{CR} < \mathbb{K}^{LF}_{No\_t}$ holds implying that both (i) the range of situations in which the firm conducts trials is more restrictive and (ii) the range of situations in which the firm does not conduct trials is larger than under laissez-faire. In this sense it is 'less likely' that the firm generates scientific knowledge.

The intuition for this deterrence effect is as follows. In the decision whether or not to conduct trials the firm compares profits of both possibilities. An important consequence of the compulsory registry is to make the firm's investment decision observable for the public. However, in a PBE with investment in trials, the firm is already expected to conduct trials. Moreover, the profits from not investing in trials increase as the registry *increases the opportunity costs* of conducting trials. The firm can now 'prove' that it is not conducting trials. Therefore, the lack of positive evidence is not penalized by the product market and not investing is more profitable. Thus, the incentives of the firm to conduct trials are reduced.

It is important to see that this deterrence effect can be substantial. Can there be situations in which clinical trials are completely deterred? Rewriting we obtain

$$\mathbb{K}^{CR} > 0 \Longleftrightarrow xqE\Pi\left(q_x = 1\right) + (1 - xq)E\Pi\left(q_x = \frac{q(1-x)}{1-xq}\right) > E\Pi\left(q_x = q\right).$$

Notice that this only holds if $E\Pi(q)$ exhibits increasing returns to quality. Otherwise, no trial is conducted (even if trials were costless).[16] The intuition for this complete deterrence effect is that the firm can now win when the trial is positive or lose when it is negative. As a result, investment in trials only happens when the firm is willing to take the risk of losing, which depends on the extent to which the conditions of product market competition reward higher quality.[17] Thus, contrary to the situation without regulation (Corollary 1), with a compulsory registry *product market conditions* matter for the firm's investment decision in clinical trials.

Corollary 2 *A compulsory registry has the following effects:*

(i) *It always has a deterrence effect on the firm's incentives to conduct clinical trials.*

(ii) *A necessary condition for the firm to be willing to conduct clinical trials is that there are increasing returns to quality in product market competition.*

The existing evidence on market performance seems to support the assumption of increasing returns to quality and, hence, the conclusion that the deterrence effect of registries will not be complete. In fact, Grabowski et al. (2002) estimated a highly skewed distribution of returns (net present values) for new drug introductions. According to their findings, the top decile of most successful new drugs accounted for a 52% of the total present value generated by all new drugs.[18] This seems to suggest that market rewards higher perceived quality at a highly increasing rate.

[16] Clinical trial costs are substantial. One single trial may cost from $1 million to more than $50 million (Simes (2002)). Moreover, postmarketing trials are very likely to be expensive because often (although not always) they are conducted against active comparators and the differences are then likely to be smaller than between a drug and a placebo (Congressional Budget Office (2006))."

[17] This parallels the findings in Dahm and Porteiro (2008) in a model of informational lobbying.

[18] Moreover, this seems to be a steady pattern of behavior over time since a similar analysis conducted for the 1980-1990

4.3 A Compulsory Registry Complemented by Trial Results Databases

"Democrats plan to introduce legislation ... require that all clinical studies be described publicly at their inception and that results be added when a trial is complete"

Couzin (2004a).

In addition to clinical trial registries a second popular policy proposal concerns clinical trial results databases. Such a database contains (a summary of the) results of completed clinical studies, regardless of outcome. An important question is to identify which strategic effects the presence of databases can generate and whether the negative incentive effects of registries extend to the situation in which registries are complemented through databases.

Notice that if the database is sufficiently comprehensive, it introduces a mechanism that solves the problem of selective reporting so that once a clinical trial is conducted, the pharmaceutical firm, if it posts results in the database, has no choice but to reveal the result of the trial. Formally, instead of (1), we have informative reporting,

$$M = \begin{cases} w & \text{if } t = w \\ \emptyset & \text{if } t = \emptyset \end{cases} . \tag{9}$$

Note also that assuming that the firm has no choice but to use the database is equivalent to imposing a regime of 'full transparency' by assumption. So we prefer to make the conservative assumption that the use of the database is a voluntary choice of the firm. Moreover, we assume that the firm does not have the capacity to credibly commit, ex-ante, that it will disclose its results to the database. In other words, this means that the decision to post information in the database is an ex-post choice of the firm, once it has observed the results of the clinical trial.

On the one hand, since there is a compulsory registry, the decision to conduct the trial is observable for the medical decision-maker who, therefore, does not have to base her behaviour on beliefs. On the other hand, the pharmaceutical firm has to decide, first, whether to conduct the trial or not and, if it conducts it, whether to disclose the results to the database or not. Let us start by solving this latter decision.

As the database is assumed to be sufficiently comprehensive, it is a mechanism that, if used, eliminates any 'ambiguity' in the report of the firm: If the firm fills in the database, this automatically implies that the outcome of the test is made public. What will the firm do? First if $t = 1$, the strategy to publicly disclose the results in the database is trivially optimal: $t = 1$ is the preferred state of the

period (Grabowski and Vernon (1994)) also found a highly skewed distribution of returns. In this study, the top two deciles accounted for more than a 70% of the total net present value.

firm and, hence, making it public can never harm its position. Second, if $t = 0$ the firm will not report the results to the database: No matter what the beliefs of the decision-maker are, there is nothing worse than reporting that the trial proved the inferiority of the firm's drug. Finally, if $t = \varnothing$, by filling in the database, the firm can show that its trial truly failed and generated an inconclusive result. If the firm did not post its results in the database, the decision-maker might suspect that the firm is hiding a negative result and update her beliefs in detriment of the firm's interest. Hence, if $t = \varnothing$, the firm will report its results to the database.

The next step is to determine the behaviour of the decision-maker. If she observes that a trial has been registered, what will she infer about the use of the database? Consider a skeptical posture giving rise to the following beliefs: "I expect the firm to fill in the database if and only if $t \neq 0$". This way the decision-maker can extract all the information even from the uninformative results.[19] It is worth noting that there cannot be an informative Perfect Bayesian Equilibrium in which less information is revealed.[20] This implies the following.

Corollary 3 *A compulsory registry complemented by a voluntary clinical trial results database can implement a regime of 'full transparency'.*

This combined policy, therefore, is successful in achieving full transparency. First, the compulsory registry makes the decision to undertake a test observable to the medical decision-maker and, secondly, the skepticism of the decision-maker towards the use of the database allows him to extract all the information from the test, irrespective of its outcome.

What is left to assess is how this enhanced transparency affects the incentives of the firm to actually invest in clinical trials. The profits of the firm from conducting a trial are given by

$$E\Pi_t = xqE\Pi\left(q_x = 1\right) + x(1-q)E\Pi\left(q_x = 0\right) + (1-x)\,E\Pi\left(q_x = q\right) - K, \tag{10}$$

while, because of the registry, when no trial is conducted profits are given by (7). Comparing yields that the former exceeds the latter if and only if

$$K \leq \mathbb{K}^{FT} \equiv xq\left[E\Pi\left(q_x = 1\right) - E\Pi\left(q_x = q\right)\right] + x(1-q)\left[E\Pi\left(q_x = 0\right) - E\Pi\left(q_x = q\right)\right].$$

[19] The behaviour of the decision-maker can be considered one of "sophisticated skepticism" as denoted by Milgrom and Roberts (1986). These authors showed that, in a hard evidence set-up, a skeptical posture of the decision-maker, in which she holds pessimistic expectations when little has been reported, can yield the full information decision. In the present paper the behaviour of the decision-maker when the firm does not fill in the database is driven by the same forces as in Milgrom and Roberts' paper.

[20] More precisely, it is straightforward to show that any other informative PBE that may exist must be payoff equivalent to the one analyzed in what follows. Details are available on request.

Proposition 5 *When there is a compulsory registry complemented by a voluntary clinical trial results database and trials are cheap enough, that is, $K \leq \mathbb{K}^{FT}$, there exists a PBE in which:*

(i) *The firm conducts trials and reports the results to the database, except when the trial provides evidence against the firm's drug.*

(ii) *The medical decision-maker considers the non-disclosure of results to the database as a proof that the outcome of the trial was negative for the firm.*

We have shown that 'full transparency' can be achieved through this combined policy. However, an important question is whether this increases or decreases the incentives to conduct clinical trials relative to the laissez-faire scenario. It is straightforward to check that $\mathbb{K}^{FT} < \mathbb{K}^{LF}_{No\_t}$. This implies that–as in the situation of a compulsory registry without database–under 'full transparency' both (i) the range of situations in which the firm conducts trials is more restrictive and (ii) the range of situations in which the firm does not conduct trials is larger than under laissez-faire. Again, it is 'less likely' that the firm generates scientific knowledge. Moreover, it can also be the case that tests are fully deterred. This will not happen, provided

$$\mathbb{K}^{FT} > 0 \Longleftrightarrow qE\Pi\left(q_x = 1\right) + (1-q)E\Pi\left(q_x = 0\right) > E\Pi\left(q_x = q\right).$$

Notice that this only holds if $E\Pi\left(q\right)$ exhibits increasing returns to quality. Otherwise, no trial is conducted (even if trials were costless).[21] Summarizing, we have the following.

Corollary 4 *A compulsory registry complemented by a voluntary clinical trial results database has the following effects:*

(i) *It can implement a regime of 'full transparency'.*

(ii) *It always has a deterrence effect on the firm's incentives to conduct clinical trials.*

(iii) *A necessary condition for the firm to be willing to conduct clinical trials is that there are increasing returns to quality in product market competition.*

This subsection has highlighted an implication of a regime of 'full transparency' that the discussion on policies to regulate clinical trials has neglected so far: There exists a trade-off between transparency

[21] The deterrence effect of the combined policy is, therefore, similar to that of a compulsory registry alone. However, it can be shown that $\mathbb{K}^{FT} > \mathbb{K}^{CR}$, whenever $\mathbb{K}^{FT}$ and $\mathbb{K}^{CR}$ are strictly positive. That is, whenever the deterrence effect is not complete, it is stronger under a compulsory clinical trial registry than under the policy that combines the registry with a results database.

and incentives to conduct clinical trials. 'Full transparency' reduces what the firm can gain by conducting trials and consequently fewer trials are conducted. Notice that this does not imply that 'full transparency' is undesirable. The optimal solution to the trade-off depends on how policy-makers value transparency versus incentives to conduct clinical trials. We will analyze a related trade-off in more detail in Section 5.

4.4 Voluntary Results Databases Complemented by Skepticism

> *"...at least in some situations, skepticism on the part of the decisionmaker ... can result in the emergence of all the relevant information and the selection of the optimal decision..."*
>
> Milgrom and Roberts (1986, p. 30).

The last subsection has shown that the objective of achieving 'full transparency' can be achieved through a combined policy of compulsory registries and voluntary results databases but that this objective necessarily comes at the price of reducing the incentives of the firms to invest in clinical trials. We analyze now the question whether one can design a regulatory regime capable of improving over this regime. We will answer this question in the positive by proposing a regulation consisting of a voluntary results database alone, that is, without the introduction of a registry.

Suppose this policy is implemented. On the one hand, since there is no registry, the decision to conduct the trial is not observable for the medical decision-maker who, therefore, has to base her behavior on beliefs. On the other hand, the pharmaceutical firm has to decide, first, whether to conduct the trial or not and, if it conducts it, whether to disclose the results to the database or not. Concerning this latter decision the same reasoning as in the last subsection applies and the firm reports the results to the database when $t \in \{\varnothing, 1\}$ and hides evidence for $t = 0$.

The next step is to determine the behaviour of the decision-maker. If she expects the firm to conduct the trial, what will she infer about the use of the database? Consider a skeptical posture generating the following beliefs: "I expect the firm to conduct a trial and to fill in the database if and only if $t \neq 0$". This way the decision-maker can extract all the information even from the uninformative results. Again, it can be shown that there cannot be an informative Perfect Bayesian Equilibrium in which less information is revealed.

Given this posture by the medical decision-maker, the profits of the firm from conducting a trial are given by (10), while when not conducting the trial profits are:

$$E\Pi_{No\_t} = E\Pi\left(q_x = 0\right). \tag{11}$$

Not conducting the trial is very expensive, as the decision-maker will be convinced that the firm not only conducted a trial, but also obtained a negative result. Comparing these expressions we have that

the pharmaceutical firm will invest in the trial if and only if $E\Pi_t - E\Pi_{No\_t} > 0$

$$\Leftrightarrow K < \mathbb{K}_t^{VD} \equiv xqE\Pi\left(q_x = 1\right) + \left(1 - x\right) E\Pi\left(q_x = q\right) - \left(1 - x\left(1 - q\right)\right) E\Pi\left(q_x = 0\right).$$

Given the monotonicity assumption, it is direct that $\mathbb{K}_t^{VD} > 0$. Finally, it is straightforward that this system of beliefs and actions forms a PBE. We have, thus, the following result.

Proposition 6 *When there is a voluntary clinical trial results database without registry and trials are cheap enough, that is, $K < \mathbb{K}_t^{VD}$, there exists a PBE in which:*

(i) *The firm conducts trials and reports the results to the database, except when the trial provides evidence against the firm's drug.*

(ii) *The medical decision-maker expects the firm to conduct the trial and considers the non-disclosure of results to the database as a proof that the outcome of the trial was negative for the firm.*

We see how the presence of a voluntary results database has very important implications for the informative equilibrium. The firm uses the database to give credibility to its message that the trial failed and reached inconclusive results. Far from being an advantage for the firm, this triggers a skeptical response from the decision-maker that turns out to be a very powerful information-acquisition tool. The decision-maker, since she knows that the firm has the capacity to give full credibility to its messages, can safely infer that, if the firm has not used this mechanism, it must be because it has a message it does not want to reveal: the outcome of the trial was conclusive and against the firm's interests. This way the decision-maker can, at equilibrium, obtain all the information from the firm and eliminate the problem of selective reporting.

We have shown how the presence of a database substantially improves the decision-maker's capacity to extract information from the firm's clinical trials. But is that achieved at the expense of deterring the firm from investing in clinical trials? Not at all. If we compare the threshold of the costs that determines the existence of an informative equilibrium in the laissez-faire scenario ($\mathbb{K}_t^{LF}$) with $\mathbb{K}_t^{VD}$, it is direct to check that $\mathbb{K}_t^{VD} > \mathbb{K}_t^{LF}$. The voluntary results database enlarges the set of parameters compatible with an equilibrium in which the firm invests in clinical trials. In this setting the skepticism on the part of the decision-maker decreases the opportunity cost of conducting trials, since the absence of any disclosure by the firm is understood as an evidence that it is withholding unwanted information. As a result, the firm is more eager to conduct a trial. We summarize this as follows.

Corollary 5 *The creation of a voluntary clinical trial results database can*

(i) *stimulate the pharmaceutical firm's incentives to conduct clinical trials; and*

(ii) *solve the problem of selective reporting.*

Notice that this policy is optimal in the sense that given 'full transparency', trials are stimulated as much as possible: 'Full transparency' fixes unambiguously the gains from a trial, while the opportunity costs of a trial (given by (11)) are reduced as much as possible.

Of course, as usual in these settings, there exists also a non-informative equilibrium in which the decision-maker optimally expects the firm not to perform a trial (and, hence, not to fill in the database). It is straightforward to check that this equilibrium is fully analogous to the one in Proposition 2 and that there is a range of parameter values for which there is multiplicity of equilibria (as $\mathbb{K}^{LF}_{No\_t} < \mathbb{K}^{VD}_{t}$ holds).

Proposition 7 *When there is a voluntary clinical trial results database and no registry, there exists a PBE in which the pharmaceutical firm does not perform a clinical trial provided trials are expensive enough, that is,* $K \geq \mathbb{K}^{LF}_{No\_t}$.

5 Medical Decisions Based Only on Published Clinical Trials

> *"...conclusions of therapeutic effectiveness based on a review of only the published trials may be seriously misleading"*
>
> Simes (1997, p. 134).

The analysis of Section 4 predicts that the decision-maker anticipates the firm's investment decision in trials and bases her decision both on published studies and on the lack of publicly available evidence in the case the trial was not positive (e.g. Proposition 1). In other words, decision-makers understand that firms might be withholding relevant information. This might be a reasonable assumption when the decision-maker is a committee conducting a systematic search of all the evidence regarding a drug, for example, in order to make a coverage decision for a health care plan or professional societies drafting practice guidelines. From a formal point of view, the analysis has made strong assumptions concerning the information the decision-maker possesses and her degree of sophistication when drawing inference from it.[22] However, the discussion concerning regulation suggests that the existence of trials that remain unpublished is often not appropriately taken into account. This problem is particularly relevant if we consider as decision-makers, for instance, practicing clinicians who make the ultimate

[22] Notice that in order to form 'correct beliefs' the decision-maker needs to know for each pharmaceutical product the perceived 'quality' q, how the firm's profits depend on this perceived 'quality' $E\Pi(q)$ and the 'quality' x of the trial. Only in that case, she will be able to form the correct expectations about the incentives of the firms to actually conduct trials.

prescribing decisions and who may have a more limited access to information. We investigate now the implications of situations where the decision-maker is ill-informed or does not have the capacity to draw the correct inference.

For this purpose, we model the decision-maker as a "naive" player in the game that does not form any expectation concerning whether a trial is carried out or not. However, if hard evidence concerning the perceived 'quality' q of the firm's product is revealed, the decision-maker's beliefs are updated accordingly (i.e., as in (5)). Moreover, if the decision-maker is certain that a trial has been conducted, she is rational, in the sense that she can update her beliefs as in (2). We offer next an informal discussion of what implications this has for our analysis. We indicate the corresponding thresholds by $\hat{\mathbb{K}}$ instead of $\mathbb{K}$ as in the previous sections.

First, under laissez-faire, given selective reporting (1), the decision-maker retains the prior belief unless a positive trial is revealed. Thus, (6) is compared to (7). This implies that in (the now unique) equilibrium trials are conducted if and only if trials are cheap enough, that is, $K \leq \hat{\mathbb{K}}^{LF} \equiv \mathbb{K}^{LF}_{No\_t}$.

Second, the conclusions concerning registries are robust: Since once a trial is registered the decision-maker is able to draw the appropriate inference, voluntary registries will not be used. Under compulsory registries, trials are conducted if and only if trials are cheap enough, that is, $K \leq \hat{\mathbb{K}}^{CR} \equiv \mathbb{K}^{CR}$. Moreover, when compulsory registries are complemented through a database the performance of tests can be observed and, hence, the decision-maker is able to have a skeptical posture. Thus, a regime of 'full transparency' can be implemented for $K \leq \hat{\mathbb{K}}^{FT} \equiv \mathbb{K}^{FT}$ and the conclusion that 'full transparency' has a deterrence effect on clinical trials is still true.

Third, without a compulsory registry the decision-maker is unable to sustain a posture of sophisticated skepticism. As a result, a voluntary results database without a compulsory registry does not allow to extract the relevant information. If no trial is conducted, (by assumption) the decision-maker is not capable of forming expectations that a trial was conducted and the firm's payoffs are given by (7). This implies that the firm has no need to reveal inconclusive trials and payoffs from conducting a trial are given by (6). Consequently, the laissez-faire equilibrium is not affected by the creation of a voluntary results database.

Summarizing, relaxing the assumption of a sophisticated decision-maker basically eliminates the so far unambiguously best regulatory recommendation: a voluntary results database without a registry no longer solves the problem of selective reporting and no longer stimulates investment in clinical trials. A simple trade-off, therefore, emerges. Under laissez-faire the decision-maker only learns about positive trials. When a compulsory registry is complemented through a database the problem of selective reporting is solved but fewer trials are conducted. The optimal solution to this trade-off depends on how society values these different alternatives.

We formalize now this basic trade-off. Proposition 8 shows that in the absence of any intervention, the incentives of the firms to conduct trials are higher but, with the combined policy the decision-makers obtain more information from the trials that are actually performed. We offer then an analysis of the type of trials involved in the trade-off which lends some qualified support for the popular demand for intervention.

In order to formalize the trade-off, notice that under laissez-faire, trials are conducted if and only if $K < \hat{\mathbb{K}}^{LF}$. In this case, the information acquired by the decision-makers is: (i) If the test is conducted and $t = 1$, then $q_x = 1$ (i.e., if the test reveals the favorable state for the firm, the decision-makers will learn it); (ii) in any other situation $q_x = q$ (no information is acquired).

In the scenario in which a compulsory registry is complemented through a voluntary database, clinical trials are carried out if and only if $K \leq \hat{\mathbb{K}}^{FT}$.[23] Here the information acquired by the decision-makers is: (i) If the test is conducted and $t = 1$, then $q_x = 1$ (again, if the test reveals the favorable state for the firm, the decision-makers will learn it); (ii) if the test is conducted and $t = 0$, then $q_x = 0$ (i.e., the decision-makers also learn when the test revealed that the true state is unfavorable to the firm); (iii) both if the test is conducted and $t = \varnothing$, and if the test is not carried out, then $q_x = q$ (no information is acquired).

In order to illustrate better how these two policies compare, we need to define the value that information has for society. Let us define by $SV(q_x|\omega)$ the value of assigning a probability q_x to state 1, conditional on ω being the true state. To be consistent with our previous analysis we stick solely to the assumption that the less uncertainty the better. This only requests that $SV(q_x = 1|\omega = 1)$ and $SV(q_x = 0|\omega = 0)$ are always higher than $SV(q_x = q|\omega = 1)$ and $SV(q_x = q|\omega = 0)$ respectively. Denoting by Δ the difference between the social value with the combined policy and in laissez-faire, the following trade-off emerges.

Proposition 8 *The most efficient scenario is:*

(i) *Complementing compulsory registries through results databases, if* $K \leq \hat{\mathbb{K}}^{FT}$*, formally*

$$\Delta = (1-q)\, x \left(SV(q_x = 0|\omega = 0) - SV(q_x = q|\omega = 0)\right) > 0.$$

(ii) *Laissez-faire, if* $K \in \left(\hat{\mathbb{K}}^{FT}, \hat{\mathbb{K}}^{LF}\right]$*, formally*

$$\Delta = -qx \left(SV(q_x = 1|\omega = 1) - SV(q_x = q|\omega = 1)\right) < 0.$$

[23] Throughout this section we consider that there are increasing returns to quality in the product market (i.e., that $\hat{\mathbb{K}}^{FT} > 0$), so that the combined policy does not fully deter clinical trials. As we already pointed out in Subsection 4.2, the existing empirical evidence (Grabowski et al. (2002)) seems to support this assumption as the one that fits best the real data on drug market performance.

(iii) *Both policies (since they are equivalent) if* $K > \hat{\mathbb{K}}^{LF}$.

Proof. See the Appendix. ■

This proposition formalizes a basic trade-off for policy-makers. When the introduction of registries and databases does not deter firms from conducting trials (i.e., if $K < \hat{\mathbb{K}}^{FT}$), then this is, undoubtedly the best scenario. No matter how we model the value of information, provided we assume that the more information, the better, this is the most efficient situation. However, if $K \in \left(\hat{\mathbb{K}}^{FT}, \hat{\mathbb{K}}^{LF}\right]$, under laissez-faire firms strategically withhold information and the introduction of registries and databases cannot improve on this situation. The intervention prevents firms from conducting trials and, consequently, reduces the amount of information available in the system. Finally, if costs are very high, then the two policies are trivially equivalent since under neither of the two, firms have incentives to invest in trials.

It is clear that the optimal solution to this trade-off depends, on one hand, on the distribution of characteristics of firms –a firm is a quadruple $(E\Pi(q), K, x, q)$– and, on the other, on how society values information. In what follows we shed some light on this trade-off by analyzing which trials are affected by the policies. To start, consider a population of firms that only differs in one dimension. That is, the relationship between profits from product market competition and perceived 'quality' (measured by $E\Pi(q)$), the 'quality' of the trials conducted (measured by x) and the cost of a single trial (K) are the same for all firms. However, pharmaceutical firms differ in the products they want to test. Some firms, for instance, may consider the possibility of conducting further trials on a product with a good position in the market (given by a high perceived 'quality' q), while other firms may be interested in pharmaceuticals with a weaker position. This heterogeneity can be very naturally embedded in the model by assuming that firms differ in the ex-ante perceived 'quality' of their drugs (q). The higher is q, the better the ex-ante position of the drug in the market. Notice that a very low or a very high q, also reflects a lower uncertainty about the drug's true quality.

Consider a continuum of firms each of which has to decide whether to invest in a clinical trial to assess the true quality of its product, or not. Firms differ in the value of q that is distributed according to a continuous density function $F(q)$ in $(0,1)$. All firms have access to the same clinical-trials technology, determined by a pair (x, K) that defines the quality of the test and its cost. Finally, in order to make the comparison meaningful, we assume that the combined policy does not fully deter all firms from conducting trials. Formally, this amounts to assuming that

$$\left(\max_{q} \hat{\mathbb{K}}^{FT}\right) > K.$$

In this setting it can be shown that:

Corollary 6 *There exist a series of thresholds,* $0 < q_1 < q_2 < q_3 < q_4 < 1$, *such that:*

(i) *Firms with $q \in (q_2, q_3]$ invest in clinical trials both with compulsory registries complemented through a voluntary database and laissez-faire.*

(ii) *Firms with $q \in [q_1, q_2)$ or $q \in (q_3, q_4]$ only invest in clinical trials in laissez-faire.*

(iii) *Firms with $q < q_1$ or $q > q_4$ never invest in clinical trials.*

Proof. See the Appendix. ■

[Insert Figure 1]

Figure 1 represents this corollary. As Proposition 8, the corollary distinguishes three cases. The first says that firms with intermediate values of q invest in trials under both policies. Therefore, as intervention allows to extract more information, laissez-faire is not optimal. This corresponds to the first case in Proposition 8. Analogously, the second and third case in the corollary and proposition, respectively, correspond to each other. When the firm's perceived 'quality' is either low or high, clinical trials are only conducted under laissez-faire and consequently this is the optimal policy. Lastly, firms with very extreme values for q are not conducting trials whatever the policy. Thus, the corollary sheds light on the trade-off from a different angle: In the absence of any intervention, the incentives of firms to conduct trials are higher, because firms with extreme perceived 'qualities'–for which the uncertainty about the firm's true quality is lower–conduct trials. However, under the combined policy decision-makers obtain more information from the trials that are actually performed, which are trials of firms with high uncertainty about the drug's true quality.

The optimal resolution of the trade-off depends, hence, on when society values additional information most. In our view, the present analysis lends important but qualified support for compulsory registries complemented through a voluntary database. This policy deters clinical trials of firms with drugs there is less uncertainty about (q is either high or low). However, society is likely to value this loss of information less than the gain of additional information about pharmaceuticals with important uncertainty (i.e., those for which the ex-ante value of q is intermediate).

This corollary can also be of interest regarding a highly controversial type of postmarketing research, the so-called "seeding trials". These trials are designed by the industry more with the aim of influencing physicians prescribing patterns rather than for scientific purposes. If we identify seeding trials as studies where firms have very little or no uncertainty about their final outcome, then the results of the Corollary 6 predict that registries will impose a strong deterrence effect on seeding trials. In this respect, therefore, our model provides unambiguous support for compulsory registries complemented through databases as a mechanism to fight such behaviour.

Building on Figure 1 one can easily identify other factors that will favour the combined policy vis-a-vis the laissez-faire:

- an improvement of the clinical-trials technology (i.e., a decrease in K and/or an increase in x), as this reduces the impact of the deterrence effect caused by the policy;
- an increase in the overall uncertainty faced by firms (i.e., an increase in the mass of firms with intermediate levels of q), as this reduces the number of firms deterred by the policy from investing in trials;
- an increase of the value society assigns to the information that a drug is worse than expected, relative to the value of knowing that it is better than expected, as this increases the informational surplus obtained from the policy.

6 Concluding Remarks

The present paper has offered a framework to analyze the incentives of drug companies to generate scientific knowledge through clinical trials and to investigate how these incentives are affected through different hotly debated regulatory environments. The fact that our model reproduces the problem of selective reporting and explains why voluntary registries failed to have the desired effects lends credibility to our analysis. We have shown that currently discussed reform proposals of implementing a compulsory registry system can be expected to have important deterrence effects on the incentives of pharmaceutical firms to conduct clinical trials: there are situations in which trials are conducted when there is no clinical trial registry and the trial is not performed when a compulsory registry is implemented. The policy implications of our model depend on whether medical decision-makers are well informed and/or sophisticated enough. If they are, then a voluntary clinical trial results database without a compulsory registry can both achieve full reporting of the results of the trials and avoid the deterrence effect. It even stimulates trials. If not, our model provides some qualified support for compulsory registries complemented through results databases.

Our analysis has assumed the best case for a clinical trial results database: there is some mechanism that solves the problem of selective reporting so that the firm, if it decides to post results in the database, must report informatively. However, since the information submitted to databases is limited, it might not be sufficient in order to check whether a given trial reported to be inconclusive is negative or inconclusive.[24] When informative reporting cannot be implemented, then databases are just another

[24] Results posting in databases conflicts with publication in peer reviewed journals. The International Committee of Medical Journal Editors will consider for publication results previously published if the posting contains less than 500 words (Laine et al. (2007)).

'channel' through which firms can report selectively.[25] In this case the results on registries are not affected by the creation of results databases. This implies that policy-makers have two policies that are candidates to be optimal: on one hand, the laissez-faire scenario and, on the other, a compulsory registry. With well informed and/or sophisticated enough medical decision-makers the laissez-faire scenario is unambiguously better, as more trials are conducted and the same information is revealed. When decision-makers are unsophisticated the following trade-off emerges between both alternatives. Under laissez-faire, there are more trials conducted but with a compulsory registry decision-makers know about the existence of trials and that some information might be hold back. However, in this scenario the case for intervention is weaker than with reliable databases, as more trials are deterred and from those trials that are conducted less is learned.

Our analysis has also assumed the best case for clinical trial registries. However, there is evidence that compliance to registries is an issue (see Zarin et al. (2005) or Sekeres et al. (2008)). If decision–makers have no access to registries or entries are not informative, then the results of the laissez-faire scenario are not altered through the introduction of registries. Thus, making sure compliance with registries and assuring access to them is a prerequisite for a meaningful public discussion on the effects of registries.[26]

Although our model is designed to capture a pharmaceutical firm's investment in clinical trials, it seems to capture (at least) some recent developments in the biotech industry, too. Recently, the United States National Human Genome Research Institute has found that genes do not act independently but that there appear to be network effects. As a result, the safety of biotech products has been questioned. According to experts, many biotech companies already conduct detailed genetic studies of their products but do not report their findings to regulators. Consequently, reporting requirements are discussed (see Caruso (2007)).

Our analysis has also implications for a recent proposal to redesign the way clinical trials are conducted. Lewis et al. (2007) propose public funding and public oversight of clinical trials in order to do justice to the public good character of trials and assure that results are fully disclosed (see also Avorn (2006)). Given that their proposal breaks the link between drug companies and researchers conducting the trials, in the language of the present paper 'full transparency' would be implemented. We have shown that this can be expected to profoundly change the incentives to conduct trials. As in Lewis et al.'s proposal, "drug companies should continue to bear a significant portion of clinical trial costs" (p. 3), the deterrence effect identified in Subsection 4.3 applies and underlines the importance of the condition under which product market competition takes place for investment in clinical trials.

[25] In this respect it is crucial how compliance is assured. Proposals include voluntary compliance, monetary penalties or public notification of noncompliance (Committee on Clinical Trial Registries (2006)).

[26] We thank an anonymous referee for raising this important issue and providing us with the references cited.

We identify, thus, a force going in the opposite direction of their prediction that the shift from a privately-supplied public good to a publicly-supplied one will correct the underprovision of clinical trials.

There are further important issues related to clinical trial registries which cannot be analyzed within the framework of the simple model of the present paper. One such issue concerns the quality of the clinical trial (denoted by x). The present paper treats this as exogenous, although it seems reasonable that the firm determines (within certain limits) the probability that the trial is inconclusive. From the perspective of the firm there will be an optimal level depending among other things on the institutional framework. Thus, it is likely that registries and databases affect this optimal choice of the firm. Consequently, the policy choice might determine how often trials are conclusive. We leave this interesting question for further research.

A second issue is related to disclosure timing. There is an important concern that the creation of a trial registry has the potential to jeopardize the commercial competitive advantage of pharmaceutical firms. As a result, the permission to delay disclosure of sensitive information has been discussed. However, it is not clear whether disclosure threatens or promotes innovation (see Palmisano (2005)). It is, hence, a challenging future research question to offer guidelines on this topic.

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A Appendix

A.1 Proof of Proposition 8

In order to compare the two policies, we compute the expected social welfare SV^e under each. Under laissez-faire we have that:

- If $K \leq \hat{\mathbb{K}}^{LF}$:

$$SV^e_{LF} = \Pr(w=1)\left[\Pr(t=1|\omega=1)\,SV(q_x=1|\omega=1) + (1-\Pr(t=1|\omega=1))\,SV(q_x=q|\omega=1)\right] + \Pr(w=0)\,SV(q_x=q|\omega=0).$$

- If $K > \hat{\mathbb{K}}^{LF}$:

$$SV^e_{LF} = \Pr(w=1)\,SV(q_x=q|\omega=1) + \Pr(w=0)\,SV(q_x=q|\omega=0).$$

Analogously, for the scenario with registries and databases we have that:

- If $K \leq \hat{\mathbb{K}}^{FT}$:

$$SV^e_{FT} = \Pr(w=1)\left[\Pr(t=1|\omega=1)\,SV(q_x=1|\omega=1) + (1-\Pr(t=1|\omega=1))\,SV(q_x=q|\omega=1)\right] + \Pr(w=0)\left[\Pr(t=0|\omega=0)\,SV(q_x=0|\omega=0) + (1-\Pr(t=0|\omega=0))\,SV(q_x=q|\omega=0)\right].$$

- If $K > \hat{\mathbb{K}}^{FT}$:

$$SV^e_{FT} = \Pr(w=1)\,SV(q_x=q|\omega=1) + \Pr(w=0)\,SV(q_x=q|\omega=0).$$

Defining $\Delta \equiv SV^e_{FT} - SV^e_{LF}$ and simplification of the resulting expressions yields the statement.

A.2 Proof of Corollary 6

It is straightforward to see that $\hat{\mathbb{K}}^{FT} < \hat{\mathbb{K}}^{LF}$. Moreover, it can be checked that:

$$\lim_{q\to 0}\hat{\mathbb{K}}^{LF} = \lim_{q\to 0}\hat{\mathbb{K}}^{FT} = \lim_{q\to 1}\hat{\mathbb{K}}^{LF} = \lim_{q\to 1}\hat{\mathbb{K}}^{FT} = 0.$$

Then, since $\left(\max_q \hat{\mathbb{K}}^{FT}\right) > K$, this necessarily implies that $E\Pi(\cdot)$ is a convex function in q_x since, otherwise, $\hat{\mathbb{K}}^{FT} < 0$. This can be used to check that, both $\hat{\mathbb{K}}^{FT}$ and $\hat{\mathbb{K}}^{LF}$ are concave functions in q.

All these facts together imply that there exist a quadruple (q_1, q_2, q_3, q_4) with $0 < q_1 < q_2 < q_3 < q_4 < 1$ such that:

- $\forall q < q_1$ it holds that $K > \hat{\mathbb{K}}^{LF} \geq \hat{\mathbb{K}}^{FT}$. Trials are never undertaken.
- $\forall q \in [q_1, q_2)$ it holds that $\hat{\mathbb{K}}^{LF} > K > \hat{\mathbb{K}}^{FT}$. Trials are only undertaken in laissez-faire.
- $\forall q \in (q_2, q_3]$ it holds that $\hat{\mathbb{K}}^{LF} > \hat{\mathbb{K}}^{FT} > K$. Trials are always carried out.
- $\forall q \in (q_3, q_4]$ it holds that $\hat{\mathbb{K}}^{LF} > K > \hat{\mathbb{K}}^{FT}$. Trials are only undertaken in laissez-faire.
- $\forall q > q_4$ it holds that $K > \hat{\mathbb{K}}^{LF} \geq \hat{\mathbb{K}}^{FT}$. Trials are never undertaken.

This completes the proof.