Clinical Trials: the Effects of Registries and Results Databases∗

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Abstract

We analyze the incentives of pharmaceutical firms to generate scientific knowledge through clinical trials and how these incentives are affected through different regulatory environments. We propose a formal model of a pharmaceutical firm’s investment in clinical trials. Our model can explain why voluntary trial registries could not solve the problem of selective reporting of trial results. We show that compulsory trial registers reduce the incentives to invest in trials. Our model predicts that, instead of registries, the implementation of a system of voluntary results databases can be a much more successful regulatory tool: (i) it can avoid the problem of selective reporting of clinical trial outcomes and (ii) it increases the incentives of the firms to invest in clinical trials. Finally, our results highlight the importance of the conditions of product market competition on the incentives to perform clinical trials and, thus, on the success of the regulations.

Keywords: interest groups, pharmaceutical firms, strategic information transmission, clinical trials, registries

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. 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: “[i]f investigators are dissuaded from doing experimental human research, the plain fact is that patients will die unnecessarily thanks to a diminution in the rate at which our clinical knowledge advances” (Horton (2006), p. 1633).

Recently, however, there have been a number of highly publicized cases in which pharmaceutical firms have selectively disclosed evidence (see e.g. Curfman et al. (2005), Avorn (2006), Pearson (2006) or Stephens (2006)). 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. To achieve this transparency there are mainly two policy proposals discussed: clinical trial registries and clinical trial results databases.

A clinical trial registry contains information on ongoing clinical studies. As a result of the growing support for registries, several voluntary registries have been created by, for example, public health authorities, the pharmaceutical industry or medical journal editors. 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 played a critical role requiring registration of clinical trials as a condition of their subsequent consideration for publication. This effort is complemented by the definition of a minimum trial registration dataset.

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

3 See the account in Horton and Smith (1999).

4 The disclosure refers to public registration of summary protocols at the initiation of all trials whose primary
by the World Health Organization aimed at standardizing the way information is made available to the public (see WHO (2006) and 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. Databases are often proposed in combination with a compulsory or voluntary trial registry. Given the scandals caused through selective publication of trial results it is surprising that (at least a part of) the pharmaceutical industry is supporting the creation of results databases.

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. 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 pharmaceutical firms 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 purpose is to affect clinical practice (phase III trials), see De Angelis et al. (2004 and 2005).

5 The US Congress, for instance, is currently considering the Fair Access to Clinical Trials Act that is an amendment to the Public Health Service Act aimed at expanding the current mandate for registration of clinical trials (see De Angelis (2005)). In Spain, the 2006 law on the rational use of drugs (“Ley 29/2006 de 26 de julio, de garantías y uso racional de los medicamentos y productos sanitarios”) explicitly requires the publication of all clinical trial results, independently of the outcome being positive or negative.

6 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://www.bio.org/bioethics/background/20050621.asp, accessed on December 3, 2006). In this document the industry commits to register ongoing trials 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 December 3, 2006). 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)).
cannot lie and forge evidence in their favor. Holding back trial results considered ‘negative’ is the so-called problem of selective disclosure of trial results which has generated the debate about reform. We propose, therefore, 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 Dahm and Porteiro (2006a) or Bennedsen and Feldmann (2006)), 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)).

We start by analyzing the effect of clinical trial registries. We look at 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 then study the effects of a compulsory registry of clinical trials. We show that a compulsory registry reduces the incentives of pharmaceutical firms to conduct trials. There are two reasons for this, negative, result. First, a registry does not affect the firm’s benefits from investing in a trial because in equilibrium medical decision-makers expect the firm to invest and to selectively report trial information. Second, the compulsory registry affects the opportunity costs of investing in trials because the firm can use the registry to ‘prove’ that it is not conducting trials. So not providing ‘positive’ trial results does not harm the firm’s position in the product market and not conducting trials becomes more profitable than without a compulsory registry. We show that there are two qualitatively different effects reducing the incentives to perform clinical trials: (i) As a result of a deterrence effect the range of situations in which clinical trials are conducted is more restrictive with a compulsory registry than without. (ii) In addition, the firm’s payoff structure from investing and not investing is profoundly altered. Contrary to the situation without compulsory registry, a trial can now both improve or worsen the firm’s situation in the product market. Hence, investment in trials depends on the extent to which product market competition rewards a higher quality. In particular, with a compulsory registry firms will only invest in clinical trials if market rewards higher quality at an increasing marginal rate (what we denote as increasing returns to quality).
Given that registries are often proposed in combination with clinical trials results databases, we analyze the strategic effects that the use of a voluntary results database can have. Databases change the way in which scientific information is disseminated by complementing peer-reviewed journal publications. However, for the incentive effects considered in the present paper databases only make a difference when they solve the problem of selective reporting. If selective reporting can not be prevented, the previous results apply directly. So we assume the best case for the policy: when a database is available, any pharmaceutical firm that decides to use the database, must credibly (fully) report its trial results.

We first focus on the effects that a results database would have in the absence of registries. We show that, in that case, the implementation of a voluntary results database can be a very powerful regulatory tool for two reasons. First, even if it is voluntary for the firm to report its results to the database, a rational decision-maker is able to extract all the information the firm has acquired through the trial. The problem of selective reporting of results is eliminated because the decision maker correctly interprets the lack of disclosure of information to the database as a proof that the trial result was against the firm’s interest. Secondly, the existence of a database, far from deterring the firm from investing in trials, fosters the firm’s incentives to conduct them.

When we study the combined policy of a compulsory registry plus a voluntary database we see that the negative effect caused by the registry still exists. However, the deterrence that the combined policy has on the incentives to conduct trials is weaker now than in the absence of a results database. So in this case clinical results databases can help to mitigate, but not eliminate, the negative incentive effect of compulsory registries.

To illustrate our approach we build two more specific models of pharmaceutical product market competition. One, in the line of Brekke and Kuhn (2006), presents a model of informational advertising of drugs; while the other, following Schmalensee (1976 and 1992), proposes a model of persuasive advertising. There are two reasons for analyzing these models. First, they allow us to show that the monotonicity assumption may arise naturally, both from informative or persuasive models of pharmaceutical advertising. Second, some of our results depend on the

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7 The role of advertising of pharmaceutical firms is highly disputed. While it is clear that marketing efforts in this industry are very high, it is not clear whether these expenditures are informative or persuasive. Advertising might be considered informative when physicians and consumers learn, for example, about new treatments. But it can be persuasive if sales agents give sample packages or product information to physicians who “may be more comfortable using a given product in a therapeutic class if they are more familiar with it” (Wang et al. 2003, p. 687). See Hurwitz and Caves (1988), Scherer (2000) and Berndt (2002) as well as the discussion and further references in Azoulay (2002).
precise conditions of product market competition and the different models of product market competition help to provide examples for situations in which these conditions might be fulfilled.

The structure of the paper is as follows. The next section presents our model of clinical trials. Section 3 analyzes the effects of registries and Section 4 of registries combined with results databases. Section 5 applies our analysis to two different models of product market competition. 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.

Treatment effects of pharmaceutical products are uncertain. Controlled clinical trials provide the most reliable evidence whether treatments are effective. As a result, pharmaceutical companies also conduct clinical trials when the drug is already approved by the FDA. An example for such a situation are trials that compare two different approaches to treatment, the so called non-inferiority trials. We will use this interpretation as an illustration for our analysis.\(^8\)

Prior to the outcome of product market competition the firm can conduct a clinical trial in order 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 \( \omega \). The interpretation is that in state 0, the firm’s 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.

\(^8\)Another motive that has elevated the importance of pharmacoeconomic analysis is 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)).
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 evidence 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, $M = \emptyset$.

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:** Firm decides whether to conduct a clinical trial.

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

**Stage 3:** Medical decision-makers update their 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, there might be situations in which it is reasonable to assume that profits are decreasing in the perceived ‘quality’
of one of the firms.\(^9\) So, it is worth mentioning that it is not important for what follows that profit are increasing in \(q\). If they were decreasing one just needs to relabel the results of clinical trials such that the firm has now an interest to reveal \(t = 0\).\(^{10}\) This would not affect the results of our analysis concerning the incentives to conduct clinical trials in Sections 3 and 4. However, increasingness is in line with the few existing empirical evidence available which comes from the antiulcer-drug market (Azoulay (2002)). Moreover, we do not impose any further structure on the profit function implying that Sections 3 and 4 apply to a wide range of models of product market competition. In Section 5 we present two models – one of persuasive advertising and one of informative advertising – where the monotonicity assumption arises naturally and in which we further elaborate the implications of compulsory registries.

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 \(\Pi(q)\). 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 \(q\)). As we will see in Section 5, the specific characteristics of the product market competition will determine which of the two scenarios prevails.

### 3 Clinical Trial Registries

We study now the incentives of pharmaceutical firms to conduct clinical trials in three different regulatory environments. First, we study a world without registries, which we label laissez-faire. We look then at compulsory and voluntary registries, respectively. 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.

\(^9\)In fact, a well known result in industrial organization – the principle of maximum product differentiation – states that in some situations firms have an incentive to choose qualities as far apart as possible. The reason is that this way price competition is relaxed. This implies that for the low quality firm profits are decreasing in its own quality. Notice, however, that that for the high quality firm the opposite is true.

\(^{10}\)What is needed for our analysis is that profits are monotonic for a small range of parameter values defined through possible variations of \(q\).
3.1 Laissez-Faire

When there are no registries, 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

\[
M = \begin{cases} 
1 & \text{if } t = 1 \\
\emptyset & \text{if } t \in \{0, \emptyset\} 
\end{cases}
\]

(1)

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

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

(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

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

(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

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

(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

\[ E\Pi_t - E\Pi_{No\_t} > 0 \iff K < K_1 \equiv xq \left( E\Pi (q_x = 1) - E\Pi \left( q_x = \frac{q(1-x)}{1-xq} \right) \right). \]

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

**Proposition 1** When there are no clinical trial registries, there exists a PBE in which the pharmaceutical firm performs a clinical trial provided trials are cheap enough, that is, \( K \leq K_1 \).

So we have seen that in a world without registries, 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)

\[ q_x = \begin{cases} 
1 & \text{if } M = 1 \\
0 & \text{if } M = 0 \\
q & \text{if } M = \emptyset
\end{cases}. \quad (5) \]

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

\[ E\Pi_t = xqE\Pi (q_x = 1) + (1-xq) E\Pi (q_x = q) - K, \quad (6) \]

and those from not performing the trial become

\[ E\Pi_{No\_t} = E\Pi (q_x = q). \quad (7) \]

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

\[ E\Pi_t - E\Pi_{No\_t} < 0 \iff K > K_2 \equiv xq (E\Pi (q_x = 1) - E\Pi (q_x = q)). \]

**Proposition 2** When there are no clinical trial registries, there exists a PBE in which the pharmaceutical firm does not perform a clinical trial provided trials are expensive enough, that is, \( K \geq K_2 \).

It is straightforward to check that \( K_1 \geq K_2 > 0 \), implying that for \( K \in [K_2, K_1] \), 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 registry 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** When there are no clinical trial registries, if trials are cheap enough in the unique
PBE clinical trials are performed—indeed of the conditions under which product market
competition takes place.

Notice two things: (i) This result only requires that profits are increasing in the “perceived”
quality of the firm’s drug (the monotonicity assumption), it holds irrespective of whether the firm
enjoys increasing or decreasing returns to quality. (ii) This result has a natural interpretation in
terms of policy design: In principle, policies that reduce the ‘price’ $K$ of clinical trials have the
potential to induce relatively more clinical trials and, thus, to generate more scientific knowledge.
An example for such a policy might be the widespread government funding of basic drug research.

### 3.2 Compulsory Registry of Clinical Trials

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

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

(8)

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

Summarizing, we have that the following holds.
Proposition 3 In the unique PBE with a compulsory clinical trial registry, the pharmaceutical firm conducts a clinical trial if trials are cheap enough, that is, \( K \leq K_R \); and decides not to generate scientific knowledge otherwise.

We have shown that both with a compulsory clinical trial registry and without registries, there is room for clinical trials to be conducted. However, an important question is under which regime incentives for clinical trials are higher. Given the monotonicity assumption of the firm’s profits in the product competition stage, we have that

\[
E\Pi(q_x = q) > E\Pi\left(q_x = \frac{q(1-x)}{1-xq}\right),
\]

and consequently,

\[K_R < K_2.\]

This implies that the range of situations in which the firm conducts trials is more restrictive with a compulsory registry. In a sense it is ‘less likely’ that the firm generates scientific knowledge. We formalize this in the following Corollary.

Corollary 2 A compulsory registry of clinical trials always has a deterrence effect on the pharmaceutical firm’s incentives to conduct clinical trials.

The intuition for the deterrence effect is as follows. In the decision whether or not to conduct trials the firm compares profits of both possibilities. The point of registries is to make the firm’s investment decision observable for the public. However, in a PBE with investment in trials, the firm is expected to conduct trials and to report the results selectively. So the firms profits from investing in trials are the same whether there is a compulsory registry or not. Consider now the profits from not investing in trials. A compulsory registry does have an effect because it increases the opportunity costs of conducting trials. The firm can now use the registry in order to ‘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 through a compulsory registry.

In addition to the deterrence effect the increase in opportunity costs introduces another qualitatively different effect. The firm can now win when the trial is positive or lose when it is not. 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 a higher quality. Thus, contrary to the situation without registry, with a compulsory registry product market conditions matter for the firm’s investment decision in clinical trials.\footnote{This parallels the findings in Dahm and Porteiro (2006a) in a model of informational lobbying.}

To see this, let us check when $K_R > 0$. If $K_R$ is negative this implies that the registry introduces a qualitatively deterrence effect: It makes the firm never be interested in investing in clinical trials (even if they were costless).\footnote{Clinical trial costs are substantial. One single trial may cost from $1 million to more than $50 million (Simes (2002)).} Remember that Corollary 1 implies that without a registry –independently of product market conditions– the firm conducts clinical trials (provided the cost of the trial does not exceed a certain threshold).

When there are compulsory registries we have that:

$$K_R > 0 \iff xqEII (q_x = 1) + (1 - xq)EII \left(q_x = \frac{q(1 - x)}{1 - qx}\right) > EII (q_x = q),$$

and this only holds provided the profit function is convex in $q$ (i.e., there are increasing returns to quality). From this reasoning it follows directly that:

**Corollary 3** A compulsory registry of clinical trials always alters the firm’s incentives to conduct clinical trials. While without registry there are always incentives to conduct clinical trials (Corollary 1), with a compulsory registry a necessary condition for the firm to be willing to conduct a clinical trial is that there are increasing returns to quality in product market competition.

### 3.3 Voluntary Registry of Clinical Trials

A hotly debated issue is whether registration in trial registries should be compulsory or voluntarily. However, one reason for the demand for compulsory registries is that participation in voluntary registries is considered too low. Why is that so? 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 4** When there is a voluntary clinical trial registry, there does not exist a PBE in
which the firm conducts trials and uses this registry.

4 Clinical Trial Results Databases

In addition to clinical trial registries a second 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 can the
presence of databases 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 pharma-
ceutical firm, if it fills in the database, has actually no choice but to reveal the result of the trial.

Formally, instead of (1), we have what we will call informative reporting:

\[
M = \begin{cases} 
  w & \text{if } t = w \\
  \emptyset & \text{if } t = \emptyset 
\end{cases}.
\]  

(9)

We start this section by assuming the best case for this policy proposal. More precisely, we
suppose that a results database is available and that, when the firm posts information about its
results in it, the problem of selective disclosure is solved so that only informative reporting is
feasible.

The other two key elements of the modelization are the timing of the decision to fill in the
database and the firm’s discretionary capacity to choose whether to use it or not. Concerning
the issue of the timing, we opt for the most conservative scenario and assume 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 pharmaceutical firm, once it has observed the results of the clinical trial. This
lack of commitment capacity also determines the second modelization choice: the database is a
voluntary choice of the firm. The medical decision-maker has no power to force the firm to fill
in the database.
In what follows we analyze, first how the laissez-faire scenario is altered when a results database is available. Then we study how the database interacts with a compulsory registry. The section concludes discussing the assumption of informative reporting and its relationship to the problems of conflict of interest and publication bias.

4.1 A Clinical Trials Results Database

We analyze now the question whether in the absence of a registry there exists a PBE in which the firm conducts trials and reports the results to the database. On the one hand, since there is no registry, the decision to do the trial is not observable for the medical decision-maker who, therefore, has to base its 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 we have said before, the database 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 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 \( t = \emptyset \), 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 against the firm. Hence, if \( t = \emptyset \), the firm will report its results to the database.

The next step is to determine the beliefs of the decision-maker. If she expects the firm to conduct the trial, which are the optimal beliefs about the use of the database? The best the decision-maker can do is to be fully skeptical: “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.\(^{13}\)

\(^{13}\) 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, the best the decision-maker can do is to interpret any ambiguity in the information disclosed by the interested parties in the way that is more damaging for the party who disclosed the information. The behaviour of the decision maker when the firm does not fulfill the database is driven by the same forces as in Milgrom and Roberts’ paper.
Given these beliefs by the medical decision-maker the profits of the firm from conducting a trial are:

\[ E\Pi_t = xqE\Pi(q_x = 1) + x(1 - q)E\Pi(q_x = 0) + (1 - x) E\Pi(q_x = q) - K, \]  

(10)

while when not conducting the trial, and given the skeptical position of the decision-maker, profits are:

\[ E\Pi_{No\_t} = E\Pi(q_x = 0). \]  

(11)

Hence, not conducting the trial is very expensive as the decision-maker will actually be convinced that the firm not only conducted it, but also obtained a negative result. Comparing these expressions we have that the pharmaceutical firm will invest in the trial if and only if

\[ E\Pi_t - E\Pi_{No\_t} > 0 \iff K < K_D \equiv xqE\Pi(q_x = 1) + (1 - x) E\Pi(q_x = q) - (1 - x (1 - q)) E\Pi(q_x = 0). \]

Given the monotonicity assumption, it is direct that \( K_D > 0 \). Finally, it is straightforward that this system of beliefs and actions forms a PBE. We have, thus, the following:

**Proposition 5** When there is a voluntary clinical trial database and no registry, 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-fulfillment of 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. First, the firm will actually use the database to give credibility to its message that the trial failed and led to 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: that 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 effect of the firm’s 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 ($K_1$) with $K_D$, it is direct to check that $K_D > K_1$ and, hence, that

**Corollary 4** The presence of a voluntary results database enlarges the set of parameters compatible with an equilibrium in which the firm invests in clinical trials.

The implementation of a results database turns out to be, therefore, a very powerful tool: (i) even if it is voluntary for the firm to report its results to it, a rational decision-maker can construct a set of beliefs that allows her to extract all the information the firm has and (ii) far from deterring the firm, the fact that not fulfilling the database is considered as a proof against the firm’s interests, fosters the firms incentives to conducts trials.

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:

**Proposition 6** When there is a voluntary clinical trial 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, $K \geq K_2$.

### 4.2 A Clinical Trial Results Database with a Compulsory Registry

So far we have seen that, in the absence of a registry, the results databases can be a very powerful tool and that the compulsory registry only deters firms from investing in trials. Suppose a compulsory registry is complemented with a voluntary clinical trial database. This implies that whenever a trial is conducted this is reflected in the public record (it is registered) and, moreover, the firm can fulfill the database and, that way, report informatively as in (9). When can we expect the firm to invest in clinical trials under these circumstances?, is the deterrence effect of the registry somehow mitigated by the results database?, will the database be used?

This last question is very easily answered in the positive: The behaviour of the firm will be analogous to the one in the previous subsection: it will report its results to the database except if $t = 0$. The behaviour of the decision-maker is also very similar, with the only difference that, since there is a registry, the decision to perform the trial is now observable.
The firm’s expected profits from investing in a trial are again given by (10). This has to be compared to the expected profits of not investing given by (7), since by not registering the trial the firm can show that is not conducting any clinical trial. Comparing yields that the former exceeds the latter if and only if

\[ K \leq \mathbb{K}_{R&D} \equiv xq \left[ E\Pi (q_x = 1) - E\Pi (q_x = q) \right] + x(1-q) \left[ E\Pi (q_x = 0) - E\Pi (q_x = q) \right]. \]

**Proposition 7** When there is a voluntary clinical trial results database combined with a compulsory registry, there exists a PBE in which the pharmaceutical firm performs a clinical trial provided trials are cheap enough, that is, \( K \leq \mathbb{K}_{R&D}. \)

Does the existence of the clinical trial results database help to mitigate the deterrence effects of the compulsory registry? Is there a deterrence effect in the first place?

Let us focus first on the qualitative deterrence effect by checking when \( \mathbb{K}_{R&D} > 0. \) Rewriting we obtain

\[ \mathbb{K}_{R&D} > 0 \iff qE\Pi (q_x = 1) + (1-q)E\Pi (q_x = 0) > E\Pi (q_x = q). \]

Again, this only holds if \( E\Pi (q) \) exhibits increasing returns to quality. Otherwise, no trial is conducted. The qualitative deterrence effect of the registry is, therefore, still present with the policy that combines registries with voluntary databases. We stick now to the case in which there is room for investment in clinical tests and study the “size” of the deterrence effect.

First, comparing \( \mathbb{K}_{R&D} \) and \( \mathbb{K}_2, \) we see that \( \mathbb{K}_2 > \mathbb{K}_{R&D} \) holds. Thus, the quantitative deterrence effect still exists as formalized in Corollary 2. But has the situation improved in comparison to the situation with a compulsory registry not complemented through a clinical trial results database? We have that

\[ \mathbb{K}_{R&D} - \mathbb{K}_R = (1-x)E\Pi (q_x = q) + x(1-q)E\Pi (q_x = 0) - (1-xq)E\Pi \left( q_x = \frac{q(1-x)}{1-xq} \right). \]

It is straightforward to see that whenever \( \mathbb{K}_{R&D} \) and \( \mathbb{K}_R \) are strictly positive, it always holds that \( \mathbb{K}_{R&D} - \mathbb{K}_R > 0 \) and, hence, that the quantitative deterrence effect is mitigated with the introduction of a database.

Summarizing we have that:

**Corollary 5** A clinical trial results database with a compulsory registry always has a deterrence effect on the pharmaceutical firm’s incentives to conduct clinical trials. In particular:
(i) If the conditions of product market competition lead to a situation with decreasing returns to quality, then the firm will never invest in clinical trials.

(ii) When there are increasing returns to quality, the firm will invest in a clinical trial if and only if its cost does not exceed the threshold $K_{R&D}$. This threshold is larger than the one with a compulsory registry not complemented through a clinical trial results database ($K_R$), but smaller than the one without a compulsory registry ($K_2$).

This subsection has shown, therefore, that complementing a compulsory registry with a clinical trial results database can be an interesting policy in two key aspects. First, if the database is comprehensive enough it can serve to eliminate the selective reporting strategy of the pharmaceutical firms, a problem that the registry itself cannot solve. This would imply that the scientific community would be able to extract valuable information from all the clinical trials that are conducted and not only from those in which the outcome favors the interest of the sponsor. Secondly, even if a voluntary clinical trial results database with a compulsory registry always has a deterrence effect on the incentives of firms to conduct clinical trials, this deterrence is of a smaller magnitude than in the scenario without a clinical trial results database.

In any case, the previous subsection has shown that the option to impose no compulsory registries and rely only on the results database is more efficient: It also eliminates the selective reporting by the firms and, instead of deterring investment in clinical trials, if fosters medical research. However, in the absence of a compulsory registry, the success of the policy relies on the decision-maker’s capacity to form beliefs optimally. In other words, for the databases alone to be successful, the decision-maker must be able to correctly form expectations about the firm’s decision to perform a trial or not. To the extent to which this belief-creation cannot be done in practical settings, then the second-best option of combining the databases with a compulsory registry can be a good compromise, as it makes the decision to perform the trial observable and rules out the need to form beliefs about the decision to invest in a clinical research.

4.3 Selective Reporting, Conflict of Interest and Publication Bias

So far in this section we have 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 fulfill the database, must report informatively as formalized in (9). While we cannot rule out that clinical trial results databases might have a way of requiring enough information in order
to check whether a given trial reported to be inconclusive is negative or inconclusive, this can be a strong assumption. Particularly, because the information submitted to databases is limited.

So it is important to indicate what the implications are when reporting is not informatively. Traditionally, reporting of trial results happened through publication in peer-reviewed journals. This “disclosure channel” has been found to be vulnerable to selective reporting. Clinical trials databases change the dissemination of clinical trial results. For instance, they unify the sources of information and make, hence, trial results more easily available. However, if informative reporting cannot be implemented, then they are just another “channel” through which firms can report selectively. In this case the results of Section 3 apply to results databases, too.

There are two further issues that are vigorously discussed and determine whether it is more reasonable to assume selective or informative reporting. The first is the 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) and selective reporting is the appropriate assumption.14 However, if measures like reporting requirements about the sponsor’s role in the study are successful, then the authors have no reason to hide evidence and informative reporting might become more realistic.

The second issue is the so-called publication bias. This 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. In the language of the present paper this is another reason for selective reporting and this argument is put forward to support the creation of trial result databases.15 In so far as publication bias can be considered the only reason for selective reporting, the installation of databases might induce informative reporting.

5 Two Models of Product Market Competition

The purpose of this section is to provide two alternative ways to model product market competition. The two models proposed satisfy that the equilibrium profits of the pharmaceutical firm are increasing in its perceived ‘quality’ $q$. This allows us to study the implications that a policy

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14 See e.g. Krimsky (1999) and the references in Davidoff (2001) for evidence about the existence of this problem.
15 See e.g. De Angelis et al. (2004).
of compulsory registry of the clinical trials would have in these markets, with the help of the results presented in the previous sections.

In the first model advertising is informative, while in the second it is persuasive. Given the disagreement concerning the nature of advertising and the different degree to which pharmaceutical markets allow price setting behavior, this approach shows that our model of clinical trials outlined in the previous section can accommodate a variety of different situations. The typical pharmaceutical market structure is oligopoly, because even a company enjoying patent protection must face competition from chemically differentiated molecules that can treat the same symptoms (see Scherer (2000) or Berndt (2002)). We restrict for simplicity to a duopoly market and index firms by $i = 0, 1$.

## 5.1 Product Market Competition with Informative Advertising

The following Hotelling model of product differentiation is built on Brekke and Kuhn (2006). In a particular therapeutic market a continuum of patients requires medical treatment. Patients are distributed uniformly on the line segment $[0, 1]$ with mass 1. A patient’s location $l \in [0, 1]$ represents disease type and/or personal characteristics. Firm $i$ sells drug $i$ at a price $p_i$. Drug 0 and 1 are located at endpoint 0 and 1, respectively. This captures the fact that drugs differ in their treatment effects and chemical compounds. The unit cost of production is $c$.

From the perspective of a physician, a patient derives the following expected utility from one unit of drug $i$:

$$U(l, i, p_i) = E(v_i) - s|l - i| - \tau p_i,$$

where $E(v_i) > 0$, $s > 0$, and $\tau \in [0, 1]$. The parameter $\tau$ represents either the copayment rate or the extent to which physicians take prices into account when they make prescription decisions. The term $s|l - i|$ reflects side-effects and other factors like contraindications that reduce the effectiveness of the drug. More precisely, there is the utility loss $s$ that multiplies the mismatch cost $|l - i|$. Finally, $E(v_i)$ represents the expected ‘quality’ or gross effectiveness of drug $i$. More specifically, we assume that

$$E(v_i) = q_i \tilde{v} + (1 - q_i)\hat{v},$$

where $\tilde{v} > \hat{v} \geq 0$. The interpretation is that a drugs effectiveness is uncertain and depends on the perceived ‘quality’ $q_i$ of firm $i$’s drug. Clinical trials have then the potential to improve a firm’s position in the market. However, when the game reaches the product market competition stage, the knowledge generated through clinical trials is taken as given.
There is also an outside treatment (e.g. surgery, physical exercise, or no treatment at all), the benefit of which is normalized to zero. It is assumed that patients cannot observe their condition nor the effectiveness of the two drugs. As a result, all patients consult a physician.

In most European countries the prices of prescription drugs are regulated by the government. We consider as benchmark this case in which price competition is absent and assume that the regulator imposes a common price $p$ for both drugs.\(^{16}\)

Suppose that there is a continuum of physicians with mass one located on the line segment following the same distribution as patients. Physicians are assumed to have the skill to identify the condition of patients, that is, the location $l \in [0, 1]$. They are perfect agents for patients. However, a priori they are uninformed about the two drugs. The marketing (detailing) activities of the two firms have the potential to carry all the relevant information about the drugs.

Denote the fraction of physicians who have been exposed to detailing by firm $i$ by $d_i$. There are three types of physicians in the market:

**Captive Physicians:** This is the fraction of physicians who have been detailed by only one firm: $d_i(1 - d_j)$. Drug $i$ will be prescribed if $U(l, i, p) \geq 0$. Patient $\tilde{l}_0 \equiv \frac{E(v_0) - sp}{s}$ (respectively $\tilde{l}_1 \equiv 1 - \frac{E(v_1) - sp}{s}$) is indifferent between drug 0 (respectively 1) and the outside treatment. So, drug 0 is prescribed to all patients with $l \in [0, \tilde{l}_0]$ and drug 1 in $l \in [\tilde{l}_1, 1]$.

**Informed Physicians:** The fraction $d_id_j$ has been exposed to detailing of both firms. With identical prices, physicians prescribe drug 0 if and only if $U(l, 0, p) \geq U(l, 1, p)$ which is the case for all patients ‘located’ close to drug 0. The patient

$$\hat{l} \equiv \frac{1}{2} + \frac{E(v_0) - E(v_1)}{2s} \tag{12}$$

is indifferent between both drugs. This implies that drug 0 is prescribed to all patients with $l \in [0, \hat{l}]$ and drug 1 to the patients in $[\hat{l}, 1]$.\(^{17}\)

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\(^{16}\)The extent of price competition differs in pharmaceutical markets. While price setting behavior is relevant in some markets, in particular the U.S., many European countries regulate the price of prescription drugs (see Scherer (2000) or Berndt (2002)). Solving the model under the assumption of price competition is analytically more involved, but the results go along the same lines.

\(^{17}\)We assume here implicitly that the price is low enough in comparison with treatment effects such that none of the firms becomes a local monopolist for a segment containing the indifferent patient, that is, $2sp \leq E(v_0) + E(v_1) - s$. 

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Non-Prescribing Physicians: The fraction of uninformed physicians who have not been detailed by any firm is \((1 - d_i)(1 - d_j)\). For this segment the outside treatment is prescribed.

This yields the following demand functions:

\[
D_0(E(v_0), E(v_1), s, \tau, p) = d_0 \left[ d_1 \hat{l} + (1 - d_1) \tilde{l}_0 \right],
\]
\[
D_1(E(v_0), E(v_1), s, \tau, p) = d_1 \left[ d_0 (1 - \hat{l}) + (1 - d_0) (1 - \tilde{l}_1) \right].
\]

Reaching a fraction \(d_i\) of physicians through detailing implies costs given by the following general cost function \(K(d_i)\) which is assumed to be increasing and convex in its argument. Firm \(i\)'s profit function is, hence,

\[
E\Pi_i(E(v_0), E(v_1), s, \tau, p) = D_i(E(v_0), E(v_1), s, \tau, p) (p - c) - K(d_i),
\]

and the firm chooses \(d_i\) in order to maximize this expression.

Consider a particular functional form for the cost of detailing: \(K(d_i) = K(d_i)^2\). This will allow us to obtain a closed-form solution for the problem the firm faces.\(^{18}\)

First, let us denote by \(\Lambda \equiv \tilde{l}_0 - \hat{l} = (1 - \tilde{l}_1) - (1 - \hat{l}) = \frac{E(v_0) + E(v_1) - s - 2 \tau p}{2s} \in (0, 1)\).\(^{19}\) With this, and solving for the optimal detailing efforts by the firms we have that:

\[
d_0^* = \frac{p - c}{K} \left( \frac{\tilde{l}_0 - \frac{p - c}{K} \Lambda (1 - \tilde{l}_1)}{1 - \left( \frac{p - c}{K} \Lambda \right)^2} \right) \in (0, 1)
\]
\[
d_1^* = \frac{p - c}{K} \left( \frac{(1 - \tilde{l}_1) - \frac{p - c}{K} \Lambda \tilde{l}_0}{1 - \left( \frac{p - c}{K} \Lambda \right)^2} \right) \in (0, 1)
\]

From here it can be obtained that

\[
E\Pi_0^* = \frac{(p - c)^2}{2K} \left( \frac{\tilde{l}_0 - \frac{p - c}{K} \Lambda (1 - \tilde{l}_1)}{1 - \left( \frac{p - c}{K} \Lambda \right)^2} \right)^2
\]
\[
E\Pi_1^* = \frac{(p - c)^2}{2K} \left( \frac{(1 - \tilde{l}_1) - \frac{p - c}{K} \Lambda \tilde{l}_0}{1 - \left( \frac{p - c}{K} \Lambda \right)^2} \right).
\]

To evaluate the effects of a policy of compulsory registry, we need to know how the profit functions of the firms depend on \(q_i\).

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\(^{18}\)Note that with the functional form chosen, we need to impose a restriction on the parameters to ensure that an interior solution exists. In what follows we assume that \(p - c < K\). It can be easily shown that this condition is sufficient to guarantee an interior solution.

\(^{19}\)If \(\Lambda\) was not positive, then the firms would enjoy a local monopoly, with no real strategic interaction.
Proposition 8 In a model of product market competition with informative advertising there are always increasing returns to quality for both firms. Formally, $\Pi_i^*$ is increasing and convex in $q_i$ for $i = 0, 1$.

Proof. We will do the proof for firm 0. The argument for firm 1 is completely analogous.

First, note that the profit function can be rewritten as:

$$E\Pi_0^* = \frac{K}{2} (d_0^*)^2.$$  

From here it follows that $\frac{\partial E\Pi_0^*}{\partial q_0} > 0$ if and only if $\frac{\partial d_0^*}{\partial q_0} > 0$.

Taking into account that $\frac{\partial d_0^*}{\partial q_0} = \frac{\bar{v} - \dot{v}}{s} > 0$ and $\frac{\partial \Lambda}{\partial q_0} = \frac{\bar{v} - \dot{v}}{2s} > 0$, it can be checked that

$$\frac{\partial d_0^*}{\partial q_0} = \frac{\bar{v} - \dot{v}}{s} \frac{p - c}{K} (1 - \frac{p - c}{2K}) \left(1 - \left(\frac{p - c}{K}\Lambda\right)^2\right) + \left(l_0 - \frac{p - c}{K} \Lambda (1 - \tilde{l}_1)\right) \left(\frac{p - c}{K}\right)^2 \Lambda > 0$$

This shows that the profits of the firm are monotonically increasing in $q_0$ and, hence, that the monotonicity assumption holds. To check the returns to quality we use the fact that $\frac{\partial^2 E\Pi_0^*}{\partial q_0 \partial q_0}$ can be rewritten as:

$$\frac{\partial^2 E\Pi_0^*}{\partial q_0 \partial q_0} = K \left( \frac{\partial d_0^*}{\partial q_0} \right)^2 + \frac{\partial d_0^*}{\partial q_0} \frac{\partial^2 d_0^*}{\partial q_0 \partial q_0}.$$  

Therefore, a sufficient condition for $\frac{\partial^2 E\Pi_0^*}{\partial q_0 \partial q_0} > 0$ is $\frac{\partial^2 d_0^*}{\partial q_0 \partial q_0} > 0$. Now, writing

$$\frac{\partial d_0^*}{\partial q_0} = \frac{\bar{v} - \dot{v} - p - c}{s} \frac{\Phi (q_0)}{K} \frac{1}{\Gamma (q_0)},$$

it can be checked that $\frac{\partial \Phi (q_0)}{\partial q_0} > 0$, while $\frac{\partial \Gamma (q_0)}{\partial q_0} < 0$. This directly implies that $\frac{\partial^2 d_0^*}{\partial q_0 \partial q_0} > 0$.

Therefore, we have shown that the profits of the firm are increasing and convex in $q_0$.

Thus, in this market, the implications of implementing a policy of compulsory registry can be summarized as:

Corollary 6 If product market competition is characterized by informative advertising:

(i) A policy of compulsory registry does not deter completely the firms from conducting medical research. There is still room for investing in clinical trials.

(ii) A combined policy of compulsory registry and a clinical trial database is strictly better than a compulsory registry alone: It can solve the problem of selective reporting and, at the same time, reduce the deterrence effect of registry over the investment in clinical trials.
5.2 Product Market Competition with Persuasive Advertising

Consider the decision of a drug formulary committee which pharmaceutical products to include in its closed formulary. A formulary can be defined as a listing of prescription medications which are covered to some degree by a health plan. Under the regime of a closed formulary, coverage is provided only for formulary drugs, and patients pay the full costs for nonformulary drugs unless an exception is granted.\(^{20}\) Such an exception requires a prior authorization which is a very time consuming process for the physician. In the U.S. these formularies have been increasingly adopted by state Medicaid programs in order to contain the rising costs of prescription drugs because high levels of patient cost sharing are either unfeasible or undesired. For simplicity we will focus on a single committee; but note that Medicaid can be considered a dominant player by market share. Notice also that formulary changes affect a physician’s prescribing pattern, not only for patients of that specific payer but also for other patients (see US General Accounting Office (1999), Scott-Levin (2001) and Wang et. al (2003)).

In theory, information about a drug’s overall value or cost-effectiveness should guide formulary placement decisions. The overall value of a drug is therefore based on two factors. For each product, on one hand, there is a review of clinical studies concerning safety and efficacy. On the other hand, when available, economic information on cost-effectiveness is taken into account. However, the provision of economic information on cost-effectiveness requires an important effort by pharmaceutical firms and as a result manufacturers comply to a different degree to this requirement. Moreover, there is scope for manipulation of these reports. In addition to clinical and economic information, other factors like rebates and low acquisition cost, as well as public opinion are believed to affect committees’ decisions (see Mather et. al (1999), Scherer (2000) and Neumann et. al (2006)).\(^{21}\) Note that public opinion is affected by detailing to physicians (which we explained in Subsection 5.1) as well as by direct to consumer advertising, which has been increasing in importance in recent years (see e.g. Huang (2000), Berndt (2002) or Brekke and Kuhn (2006)).

Suppose that the committee’s decision depends on published clinical trial studies and ‘per-

\(^{20}\)Drug formularies can be distinguished as being open, incentive based, or closed. In the first category, patients are not penalized financially if they are prescribed nonformulary drugs and sometimes there are additional incentives for physicians to prescribe formulary drugs. An incentive-based formulary covers nonformulary drugs but requires a higher copayment than for formulary drugs.

\(^{21}\)“There may be pressure to cover certain therapies even if they have unfavorable cost-effectiveness ratios. This may be a particular concern for Medicaid programs, which may be more sensitive to public pressure than private plans” (Neumann et. al (2006), p. 35).
suaision efforts’ by the firms. Effort comprises all the other factors described above different from clinical trials, and we might think of it as containing persuasive advertising. From the above, it is clear that for a drug to have a positive value for the committee, clinical trial results must be complemented through other activities and vice versa. Moreover, assume that there is a pivotal committee member who has to choose exactly one product to include in the formulary. She has some prior experience with products of both manufacturers which affect her decision. Let this experience be captured by \( \theta \in [0,1] \), which is unknown to the firms. However, firms consider that each is equally likely to be favored so that they believe that \( \theta \) is uniformly distributed on \([0,1]\). More precisely, assume that the committee member assigns to the two products the following values

\[
U_0(q_0, e_0, \theta) = q_0 e_0 \theta \quad \text{and} \quad U_1(q_1, e_1, \theta) = q_1 e_1 (1 - \theta),
\]

where \( e_i \in \mathbb{R} \) \((i = 0, 1)\) is the effort of firm \( i \) and \( q_i \) is the level of perceived ‘quality’ of its product according to published clinical trials. It follows that

\[
U_0(q_0, e_0, \theta) \geq U_1(q_1, e_1, \theta) \iff \theta \geq \hat{\theta} \equiv \frac{q_1 e_1}{q_0 e_0 + q_1 e_1}.
\]

Thus, firm 0’s probability to get its product on the drug formulary is \( \Pr(\theta \geq \hat{\theta}) = 1 - \hat{\theta} = \frac{q_0 e_0}{q_0 e_0 + q_1 e_1} \) \footnote{See also Dahm and Porteiro (2006b) and Corchón and Dahm (2006).}

Accordingly, given a level of perceived ‘quality’ \( q_i \), firm \( i \)’s expected profit from exerting effort is

\[
\Pi_i(q_i, q_j, e_i, e_j) = \frac{q_i e_i}{q_0 e_0 + q_1 e_1} V_i - e_i,
\]

where \( V_i \) is the value from being included in the drug formulary and the costs of exerting efforts are assumed to be linear. This value might a function of total unit sales \( S \), the (exogenous) price \( p \) and constant per unit cost \( c_i \), so that \( V_i = S(p - c_i) \). It is straightforward to analyze the equilibrium of this game (see e.g. Dahm and Porteiro (2006) or the references therein). Assuming that effort levels are chosen simultaneously and that both firms have the same cost, equilibrium profits simplify to

\[
\Pi_i(q_i, q_j, e_i^*, e_j^*) = \left( \frac{q_i}{q_0 + q_1} \right)^2 V.
\]

Note that for all \( q_j \neq 0 \), this expression is a strictly increasing function of \( q_i \). Notice also that the marginal returns to quality are determined by the ex-ante differential in perceived ‘qualities’. In particular, \( \Pi_i(q_i, q_j, e_i^*, e_j^*) \) presents increasing returns to quality if and only if \( q_i < \frac{q_j}{2} \). So an
increase in the firm’s perceived quality has a large effect when the firm drug’s quality was initially perceived to be very low in comparison to its competitor’s. This, in turn, has implications for the implementation of a policy of compulsory registry:

**Corollary 7** If product market competition is characterized by persuasive advertising:

(i) If initially, the “perceived” quality of the two firms is relatively similar (i.e., \( \min\{q_0, q_1\} > \frac{\max(q_0, q_1)}{2} \)) then the compulsory registry will completely deter firms from investing in clinical trials.

(ii) When the “perceived” quality of the two firms is sufficiently unbalanced (i.e., \( \min\{q_0, q_1\} < \frac{\max(q_0, q_1)}{2} \)), a policy of compulsory registry will only deter from investing in clinical trials the firm that is perceived as high-quality.

This corollary clearly illustrates the trade-off that the firms face when deciding to engage in costly clinical trials in the presence of a compulsory registry. Now the firm, if it carries out the test will win when the trial is positive and lose when it is not. Therefore, only if the firm’s initial situation is sufficiently weak, it will be interested in taking the risk of doing a clinical trial to try to improve its position in the market. In this case, therefore, the qualitative deterrence of the compulsory registries has an asymmetric impact in the market, affecting only the ex-ante dominant firm.

**Remark 1** This model can be reinterpreted as a variant of Schmalensee’s model of promotional advertising competition (Schmalensee (1976 and 1992)). In this model advertising affects firms’ demand functions and increases thus firms’ market share. See also Konrad (2002) for a related model of promotional competition for doctors through persuasive ‘detailing’.

### 6 Concluding Remarks

The present paper has offered a formal analysis of the generation of scientific knowledge through the performance of clinical trials. We have shown that currently discussed reform proposal of implementing a compulsory registry system can be expected to have important negative 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 fact that our model can explain why voluntary registries failed to have the desired effects lends credibility to our analysis. In this respect it is interesting to note that within the framework of the current model there are two ways to rationalize the pharmaceutical industry’s support for clinical trial registries complemented through a results database. The industry’s support is surprising in view of the problem of selective reporting of trial results because databases are supposed to prevent selective reporting. First, there is the cynical view that if the industry considers that informative reporting can not be implemented anyway, then databases can be offered without harm and may serve to obtain a voluntary registry—at least for some trials in return. But second, there is another more interesting explanation. Our analysis has shown that, if the database is sufficiently comprehensive so as to avoid selective reporting, and the decision-maker is capable of forming correct expectations about the firm’s decision to fulfill the database, then firms will, at equilibrium, decide to use the databases.

There are, however, 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 (2006)). It is, hence, a challenging future research question to offer guidelines on this topic.
References


