

25 Since randomized controlled clinical trials provide the most reliable way to test the efficacy
26 and safety of medical treatments, they constitute one of the main tools of scientific
27 medicine. Consequently, a first goal in the design of the incentives to conduct medical
28 research is to stimulate clinical trials as much as possible [1, 2]. Recent scandals, however,
29 in which pharmaceutical firms have selectively disclosed evidence on marketed drugs, have
30 generated a controversial debate about the appropriate design of the environment in which
31 clinical trials take place and underlined as a second goal the need to achieve greater
32 transparency in clinical trials [3].

33

34 To achieve this transparency there are mainly two policy proposals discussed: clinical trial
35 registries (which contain information on ongoing clinical studies) and clinical trial results
36 databases (which contain a summary of the results of completed clinical studies, regardless
37 of outcome). Advocates of these policy proposals argue that if clinical trials were registered
38 in a systematic way at their inception and followed by posting of summary results for the
39 trial, then the full range of clinical evidence would become part of the public record. This
40 way a complete picture would be provided and selective reporting of clinical trial data
41 would be not possible [101].

42

43 The present report draws upon prior work by the authors [4] and aims at contributing to the
44 debate about the appropriate design of the incentives to conduct medical research by
45 offering a theoretical framework of a firm's decision to engage in clinical trials. In a
46 nutshell, our analysis starts from the fact that clinical trials constitute an investment in
47 information by pharmaceutical firms. Depending on the specific situation at hand, the firm
48 might be unconstrained in this decision (e.g. some postmarketing studies are industry
49 initiated) or required to carry out a given trial (e.g. the so-called postmarketing
50 commitments).¹ For simplicity, our analysis supposes that the firm is completely
51 unconstrained in its decision. It is, however, worth to point out that, even when there are
52 constraints, it is important to take into account the incentives of the firm, as it retains
53 discretion concerning, for instance, the design of clinical trials [6].

¹ See the article by Glasser and colleagues [5]. See also the Expert Commentary & Five-Year View below.

54

55 Registries and databases affect the return on this investment in trials by restricting the way
56 in which drug companies transmit knowledge to medical decision-makers. They are,
57 therefore, likely to affect the firm's investment in information, that is, the decision whether
58 or not to conduct clinical trials.

59

60 Our framework reproduces incentives for selective reporting and allows to analyze different
61 disclosure policy regimes. Our results confirm that a combination of registries and
62 databases has the potential to increase transparency about the trials conducted and provide
63 the desired complete picture of a particular health intervention. However, we also enrich
64 the ongoing discussion by pointing out that the introduction of registries is very likely to
65 have a side effect that to the best of our knowledge has not been mentioned before. It is
66 likely to reduce the incentives of pharmaceutical firms to engage in clinical trials.² In other
67 words an improvement with respect to the second goal might come at the cost of worse
68 performance with respect to the first. This does not imply that the introduction of registries
69 is undesirable but an informed policy choice must take into account all likely consequences
70 of regulatory action and balance both goals.

71

72 **Clinical Trials and Incentives for Selective Reporting**

73

74 The problem of selective publication of clinical trial results has already been recognized
75 long ago and almost twenty years ago the first voices were raised demanding to require
76 registration of all clinical trials prior to initiation [7]. Over the last years there have been a
77 number of highly publicized cases in which pharmaceutical companies have been accused
78 of suppressing adverse findings from clinical testing that have put this problem into the
79 spotlight [8-12]. Despite the difficulty in quantifying the impact of selective reporting due

² Notice that this is a very different argument from the concern that transparency might make proprietary and confidential information available which might enable competitors to copy innovations and prevent the industry from recouping their investments. See the report by the Committee on Clinical Trial Registries [101].

80 to the lack of data from unpublished trials, the existing evidence suggests that it is, indeed,
81 a relevant problem.³

82

83 Selective reporting is far from being the only problem. Outcome reporting biases include
84 study design biases, publication bias associated with the source of funding for the study and
85 other questionable practices [14-16].⁴

86

87 Our analysis focuses on the issue of selective reporting which has generated the debate
88 about reform and sidesteps these other problems. We make the benchmark assumption that
89 the scope of pharmaceutical firms to manipulate trial results is limited in the following way.
90 Companies can hold back information about unfavourable results but they cannot lie and
91 forge evidence in their favour, i.e., they cannot indicate that certain desirable treatment
92 effects exist when they do not.

93

94 We adopt a game-theoretical approach and propose a two-stage game of hard evidence
95 (following the set up proposed by Milgrom [18]) as the appropriate model of clinical trials
96 and information transmission from pharmaceutical firms to the public. In the first stage
97 companies choose whether or not to conduct clinical trials. Trial results can be negative,
98 positive or inconclusive [3], and the publication of trial results affects product market
99 competition in the second stage. We model the second stage through a very mild
100 monotonicity assumption saying that it is advantageous for companies to publish positive
101 results. This assumption is natural as it ensures that companies have an economic
102 motivation to conduct trials.⁵

103

104 Our model predicts that without disclosure requirements firms conform to the behaviour
105 that triggered the before mentioned scandals and report their trial results selectively. In

³ Turner and colleagues have analyzed selective reporting 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, only 3 out of 36 of those viewed as negative (or questionable) were published as non positive [13].

⁴ See the report by Dickersin [102] for an extensive review of the problems associated to the reporting of trial results and the article by Chan and colleagues to determine the prevalence of incomplete outcome reporting in published reports of randomized trials [17].

⁵ Moreover, this assumption is in line with the existing evidence in, for instance, the antiulcer-drug market [19].

106 other words, companies do have incentives to hide negative results. This prediction lends
107 credibility to the set-up of our model and to the additional findings described below.

108

109 **Voluntary or Mandatory Trial Registries?**

110

111 A clinical trial registry contains information on ongoing clinical studies. The objective is to
112 ensure that the complete picture of a particular health care intervention is accessible to all
113 those involved in health care decision making. Advocates for registries argue that they will
114 improve transparency of the research conducted and ultimately strengthen the validity and
115 value of the scientific evidence base.

116

117 As a result of the growing support for registries, several voluntary registries have been
118 created by, for example, public health authorities and the pharmaceutical industry.
119 However, given the limited success of these voluntary registries in solving the problem of
120 selective reporting of clinical trials [3], policy proposals turned then towards the promotion
121 of compulsory registration of all clinical trials.⁶

122

123 Our framework offers an explanation for the limited use of voluntary registries, which
124 again validates the credibility of our approach. Our formal analysis of the interaction
125 between pharmaceutical firms and decision-makers reveals the following. On the one hand,
126 if the registry is used, selective reporting is difficult. On the other hand, when the registry is
127 not used, a negative trial can be hidden, while lack of registration does not jeopardize the
128 publication of a positive trial. Given that avoiding registration of a trial has no
129 consequences for companies, it creates a strong incentive to “wait and see”. In other words,
130 voluntary registries offer no advantage to pharmaceutical firms, and will not be used.

131

132 Our game-theoretical approach also sheds light on the effects of compulsory registration.
133 First, it predicts that the introduction of registries cannot solve the problem of selective

⁶ See the important role played by the International Committee of Medical Journal Editors in this respect [3, 20].

134 reporting completely and, second, it is very likely to have a side effect that to the best of
135 our knowledge has not been mentioned before. We explain both in what follows.

136

137 Registries cannot solve the problem of selective reporting completely because there is no
138 obligation to publish the results of negative trials. Registries only make the firm's
139 investment decision observable to the public. This limits the capacity of companies to hide
140 clinical trial results because decision makers have now further information and know which
141 trials are conducted. The lack of published trial results might trigger the suspicion that the
142 firm is withholding information—but it creates no certainty that this is the case, since the
143 trial might have been inconclusive. If, however, negative results are (voluntarily) published,
144 decision makers know that the trial was conclusive and negative, which is the worst
145 scenario for the firm. Thus, even with compulsory registries, selective reporting should be
146 expected.

147

148 It is important to understand that there is a side effect. As just explained, registration of a
149 trial does not create certainty whether a registered trial whose results were not reported was
150 inconclusive or negative. But it eliminates all suspicions concerning which companies are
151 conducting trials. Without a registry, even if a company does not conduct trials, decision
152 makers might suspect they do. With a registry there is no such suspicion and, therefore, not
153 conducting trials becomes more profitable relative to conducting them. Hence, compulsory
154 registration distorts the incentives to conduct trials relative to the situation without
155 regulation and acts as a deterrence mechanism reducing the incentives to engage in clinical
156 studies. Although this deterrence effect can be substantial, as we will explain now this
157 result does not imply that the introduction of registries is undesirable from a policy
158 perspective.

159

160 **Can Registration of Clinical Trial Results Be a Useful Regulatory Tool?**

161

162 A second policy proposal concerns the use of clinical trial results databases in combination
163 with mandatory trial registries. A clinical trial results database contains a summary of the
164 results of completed clinical studies, regardless of outcome. Recent legislation in the U.S.

165 (the Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801))
166 requires in addition to mandatory clinical trial registration new requirements for results
167 reporting at ClinicalTrials.gov [21, 22]. In what follows we identify the strategic effects of
168 such a combined policy and analyze whether the deterrence effect of registries extends to
169 the situation in which they are complemented through databases.

170

171 Notice that databases must be sufficiently comprehensive in order to have the potential to
172 dissuade companies from strategically disclosing information. In other words, the data
173 posted in the database must be detailed enough for an informed reader to draw the correct
174 inferences about the trial outcome. Related to this is the issue of compliance and
175 enforcement. Firms might try to “obscure” the picture by failing to post all the required
176 information or by posting it in such a way that the interpretation is ambiguous. To the
177 extent that these are relevant problems, the introduction of databases cannot be expected to
178 make a difference and improve upon a policy consisting only of mandatory registries.⁷

179

180 In our study we abstract from these two concerns in order to understand whether, in a best-
181 case scenario, a policy of mandatory registries complemented by databases can be expected
182 to achieve transparency in clinical trials. Our results show that this is indeed the case and
183 that this combined policy can solve the problem of selective reporting. The compulsory
184 registry provides medical decision makers with key information as all trials that are being
185 conducted are made public. This gives an important advantage to decision makers. They
186 can be sceptical and interpret failure of results posting in the database as an attempt to
187 conceal negative evidence. Scepticism can induce full transparency and, hence, rule out the
188 problems associated with selective disclosure of evidence on marketed drugs.

189

190 It is important to see, however, that “full transparency” in clinical trials comes at a cost. As
191 “full transparency” is achieved based on the introduction of compulsory registries, the
192 incentives to conduct trials are distorted and the side effect mentioned earlier can be
193 expected to be present. The registry reduces the firm’s gains from clinical trials and fewer

⁷ The articles by Zarin and colleagues and Sekeres and colleagues provide evidence suggesting that, at least for registries, compliance is often a relevant problem [23, 24]. The compliance mechanisms discussed range from voluntary compliance and monetary penalties to public notification of noncompliance [103].

194 trials are conducted. Thus, an important trade-off emerges: Obtaining more precise
195 information about the trials conducted comes at the expense of deterring some trials. This
196 makes difficult to draw a clear-cut recommendation. Whether is better not to regulate or
197 complement a compulsory registry through a database depends on how society values more
198 trials (without disclosure requirements) versus more precise information (with disclosure
199 requirements).

200

201 Our framework offers a deeper analysis of this trade-off and provides some qualified
202 support for the latter. The reason is as follows. We distinguish health care interventions by
203 how much is known about them before the clinical trial is conducted. This allows us to
204 show that the combined policy is very likely to deter clinical trials on drugs for which there
205 is little uncertainty. In other words, the information gained with the combined policy relates
206 to drugs society knows less about. Studies with very little or no uncertainty about their final
207 outcome might be interpreted as the highly controversial “seeding trials”. These are trials
208 designed by the industry more with the aim of influencing physicians prescribing patterns
209 rather than for scientific purposes. Our results can, thus, be interpreted as predicting that
210 “seeding trials” are likely to be deterred most, lending important additional support for a
211 policy of compulsory registries complemented through databases.

212

213 **Conclusions**

214

215 Registries and results databases do not have side effects ... or do they? Little is known
216 about the effects of these policies. Our analysis is a first step showing that registries and
217 results databases alter the incentives of pharmaceutical firms in important ways but more
218 research is needed. First, it is important to know how robust our findings are. We are aware
219 of only one other relevant study. In independent work, Henry provides a general model of
220 information search and transmission. Applied to clinical trials arises a very different model
221 from ours which also supports a disincentive effect of disclosure requirements [25].
222 Second, systematic empirical analysis should confirm the theoretical analysis and quantify
223 the effects. Interestingly, Henry also presents some suggestive, but preliminary, evidence
224 for a disincentive effect of disclosure rules for clinical trials. Third, there are additional

225 issues that merit a closer look. Our current research tries to determine whether registries
226 and databases affect pharmaceutical firms' investment in R&D. Examples of further
227 important questions are whether and in which direction these policies affect trial design and
228 which dynamic effects arise (e.g. related to the concern that disclosure rules jeopardize the
229 commercial competitive advantage of pharmaceutical firms).

230

231 **Expert Commentary & Five-Year View**

232

233 As mentioned in the Introduction, a pharmaceutical firm's discretion of whether to initiate a
234 clinical trial differs depending on the situation at hand. An important class of clinical trials
235 for which a firm retains considerable discretion and that is closely linked to the scandals of
236 selective reporting are postmarketing studies. This is the fastest-growing area of clinical
237 research today. At an annual growth rate of 23%, industry investment in postmarketing
238 research is expected to top \$12 billion in 2007 [104]. According to a study from the Tufts
239 Center for the Study of Drug Development, between 1998 and 2003 the FDA requested
240 postmarketing commitment studies in 73% of the approvals for new drugs [26]. Given that,
241 for instance, pharmaceutical firms face strong pressure to provide clinical and economic
242 data that justify inclusion in drug formularies [24] or that postmarketing studies are also
243 conducted upon approval of a new drug in order to study the compound for potential use for
244 other medical conditions, pharmaceutical companies face strong incentives to conduct these
245 studies and it seems reasonable that they maintain their importance in the near future.

246

247 Over recent years, governments around the world have begun to legislate mandatory
248 disclosure of all trials. Databases have often been proposed in combination with a
249 compulsory trial registry. For example, on September 27, 2007, President Bush signed into
250 law The Food and Drug Administration Revitalization Act, which contains mandatory
251 registration and results reporting requirements [28]. Another initiative, the Fair Access to
252 Clinical Trials Act which is an amendment to the Public Health Service Act, did not
253 become law but this did not end the discussion. In addition, in other parts of the world
254 similar rules are discussed. For instance, several European countries have established
255 disclosure rules in the form of registries or results databases, while others are discussing

256 such rules. In many cases legislation must be followed by rulemaking. It seems therefore
257 reasonable that mandatory registries and result databases remain an important part of
258 reform in clinical trials.

259

260

261 **Key Issues**

- 262 • Several scandals of selective reporting of evidence on marketed drugs.
- 263 • Need of intervention to improve research transparency.
- 264 • We should not expect voluntary registries being used.
- 265 • Mandatory registries do not solve selective reporting and disincentive firms from
266 doing trials.
- 267 • A combined policy of mandatory registries and results databases can achieve full
268 transparency- the ideal of the medical literature.
- 269 • A combined policy of mandatory registries and results databases can disincentive
270 firms from devoting resources to seeding trials.
- 271 • For any policy to work it is necessary that all parties involved in medical decision
272 making commit credibly to make decisions based on the information publicly
273 available.
- 274 • More research is necessary.

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