The Economics of Investment in Clinical Trials

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Clinical Trials

- test the efficacy and safety of medical treatments;
- inform medical decision-makers;
- May 20, 2005;
- “[if] 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);
- => appropriate design of the incentives to conduct clinical research important.
Selective Reporting

- scandals of selective reporting;
- greater transparency in clinical trials is needed;
- mainly two policy proposals discussed:
  1. clinical trial registries;
  2. clinical trial results databases.
This Paper

- provides a framework to analyze incentives to conduct trials;
- analyzes effect of policies on incentives;
- three key findings:
  1. full transparency has a deterrence effect;
  2. but can be implemented;
  3. policy implications depend on degree of sophistication of medical decision-makers.
A Model of Clinical Trials

- firm produces drug of perceived ‘quality’ $q \in (0, 1)$;
- possibility of so-called ‘non-inferiority trial’:
  - two states of the world $\{0, 1\}$;
  - probability that the firm’s drug is equivalent is $q > 0$;
  - clinical trial: $(K > 0, x \in (0, 1])$, result $t$ is hard evidence;
  - $\Rightarrow$ positive, negative or inconclusive trial;
- firm’s report or message is $M \in \{\omega, \emptyset\}$
- $\Rightarrow$ selective reporting possible, forging evidence not.
A Model of Clinical Trials II

Timing:

Stage 1: $F$ decides whether to conduct trial.

Stage 2: $F$ sends message $M$ to medical $DM$.

Stage 3: $DM$ updates her belief about the perceived ‘quality’ of the firm’s product to $q_x$.

Stage 4: Product market competition takes place.

**Monotonicity Assumption:**

$E\Pi(q)$ strictly increasing in its perceived ‘quality’ $q$. 
“The pharmaceutical industry has systematically misled physicians and patients by suppressing information on their drugs...”

Representative Henry Waxman (D-CA) at a hearing.
Laissez-Faire II

- hard evidence \(\Rightarrow\) \(F\) hides negative trials;
- \(DM\) expects selective reporting;
- \(E_\Pi_t = xqE_\Pi (q_x = 1) + (1 - xq) E_\Pi (q_x = \frac{q(1-x)}{1-xq}) - K;\)
- \(E_\Pi_{No_t} = E_\Pi (q_x = \frac{q(1-x)}{1-xq});\)
- \(E_\Pi_t - E_\Pi_{No_t} > 0 \iff K < K_t^{LF};\)
- \(K_t^{LF} \equiv xq \left(E_\Pi (q_x = 1) - E_\Pi \left(q_x = \frac{q(1-x)}{1-xq}\right)\right);\)
- **Proposition 1** There exists a PBE in which a clinical trial is conducted if and only if \(K \leq K_t^{LF}.\)
“Honest reporting begins with revealing the existence of all clinical studies, even those that reflect unfavorably on a research sponsor’s product. ... We are far from this ideal at present ...”

Full Transparency II

- Suppose full transparency;

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

\[ E\Pi_{No_t} = E\Pi(q_x = q); \]

\[ E\Pi_t - E\Pi_{No_t} > 0 \iff K < \mathbb{K}^{FT}; \]

\[ \mathbb{K}^{FT} \equiv xq [E\Pi(q_x = 1) - E\Pi(q_x = q)] + x(1 - q) [E\Pi(q_x = 0) - E\Pi(q_x = q)]; \]

- **Proposition 2** In the unique PBE a clinical trial is conducted if and only if \( K \leq \mathbb{K}^{FT}. \)
Corollary 1  *The introduction of ‘full transparency’ in clinical trials always has a deterrence effect on the pharmaceutical firm’s incentives to conduct clinical trials.*

- increases the opportunity costs;

- *product market conditions* matter for the firm’s investment decision in clinical trials;

- needed: increasing returns to quality;
1st Main Result

There exists a trade-off between transparency and incentives to conduct clinical trials.
Policies

1. Voluntary Registries
2. Compulsory Registries
3. Compulsory Registries + Voluntary Trial Results Databases
4. Voluntary Trial Results Databases + Skepticism
“Democrats plan to introduce legislation ... require that all clinical studies be described publicly at their inception and that results be added when a trial is complete”

Couzin (2004a).
Compulsory Registries & Voluntary Results Databases II

- databases:
  - sufficiently comprehensive;
  - voluntary ex-post choice.

- database used if $t \in \{1, \emptyset\}$;

- optimal beliefs $DM$: sophisticated skepticism (Milgrom and Roberts (1986));

- Corollary 2 A compulsory registry complemented by a voluntary clinical trial results database can implement a regime of ‘full transparency’.
2nd Main Result

Full transparency—the ideal of the medical literature—can be implemented through a compulsory registry complemented by a voluntary clinical trial results database.
Voluntary Results Databases & Skepticism II

- database used if $t \in \{1, \emptyset\}$;
- optimal beliefs $DM$: sophisticated skepticism (Milgrom and Roberts (1986));

\[ E\Pi_{No_t} = E\Pi (q_x = 0); \]

\[ K_t^{VD} \equiv xqE\Pi (q_x = 1) + (1 - x) E\Pi (q_x = q) - (1 - x (1 - q)) E\Pi (q_x = 0); \]

**Proposition 3** If $K < K_t^{VD}$, there exists a PBE in which the medical decision-maker extracts all the information from the firm.
Corollary 3  The creation of a voluntary clinical trial results database can

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

(ii) solve the problem of selective reporting.

there exists also a non-informative equilibrium;

there is multiplicity of equilibria if \( K \in [K_{No_t}^{LF}, K_t^{VD}] \);
“...conclusions of therapeutic effectiveness based on a review of only the published trials may be seriously misleading”

Medical Decisions Based Only on Positive Clinical Trials II

- $DM$ ill-informed or simply not sophisticated enough;
- modelled as a naive automaton–not as a player;
- informal discussion of what implications:
  1. robustness of two main results so far;
  2. voluntary results databases no longer allow to extract all information;
- a simple trade-off emerges:
  - laissez-fair vs.
  - compulsory registry complemented through a database.
3rd Main Result

Policy implications depend on degree of sophistication/information of medical decision-makers:

- Fully informed $\Rightarrow$ voluntary results databases;
- Not able to be ‘skeptical’ $\Rightarrow$ some qualified support for compulsory registries complemented through results databases.
Conclusions: This Paper

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- analyzes effect of policies on incentives;
- three key findings:
  1. full transparency has a deterrence effect;
  2. but can be implemented;
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Conclusions II

- assumed best case for a clinical trial results database;
- recent developments in the biotech industry;
- Lewis et al. (2007) propose public funding and public oversight of clinical trials;
- future research:
  1. endogenous quality of clinical trials;
  2. disclosure timing and commercial competitive advantage;