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;
  - $=>$ positive, negative or inconclusive trial;
  - firm's report or message is $M \in \{\omega, \emptyset\}$
  - $=>$ 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.

Laissez-Faire

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

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

Laissez-Faire II

- hard evidence $=>$ F hides negative trials;
- DM expects selective reporting;
- $E\Pi_t = xqE\Pi\left(q_x = 1\right) + \left(1 - xq\right) E\Pi\left(q_x = \frac{q(1-x)}{1-xq}\right) - K$;
- $E\Pi_{No\_t} = E\Pi\left(q_x = \frac{q(1-x)}{1-xq}\right)$;
- $E\Pi_t - E\Pi_{No\_t} > 0 \Leftrightarrow K < \mathbb{K}_t^{LF}$;
- $\mathbb{K}_t^{LF} \equiv xq\left(E\Pi\left(q_x = 1\right) - E\Pi\left(q_x = \frac{q(1-x)}{1-xq}\right)\right)$;
- **Proposition 1** *There exists a PBE in which a clinical trial is conducted if and only if* $K \leq \mathbb{K}_t^{LF}$.

Full Transparency

"Honest reporting begins with revealing the existence of all clinical studies, even those that reflect unfavorably on a research sponsor's product. ... We are far from this ideal at present ..."

De Angelis et al. (2004), p. 477.

Full Transparency II

- suppose full transparency;
- $E\Pi_t = xqE\Pi\left(q_x = 1\right) + x(1-q)E\Pi\left(q_x = 0\right) + (1-x)\,E\Pi\left(q_x = q\right) - K$;
- $E\Pi_{No\_t} = E\Pi\left(q_x = q\right)$;
- $E\Pi_t - E\Pi_{No\_t} > 0 \Leftrightarrow K < \mathbb{K}^{FT}$;
- $\mathbb{K}^{FT} \equiv xq\left[E\Pi\left(q_x = 1\right) - E\Pi\left(q_x = q\right)\right] + x(1-q)\left[E\Pi\left(q_x = 0\right) - E\Pi\left(q_x = q\right)\right]$;
- **Proposition 2** *In the unique PBE a clinical trial is conducted if and only if* $K \leq \mathbb{K}^{FT}$.

Full Transparency III

- $\mathbb{K}^{FT} < \mathbb{K}^{LF}_{No\_t} < \mathbb{K}^{LF}_{t}$;
- **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;

1^{st} 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

Compulsory Registries & Voluntary Results Databases

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

Couzin (2004a).

Compulsory Registries & Voluntary Results Databases II

- databases:
  - sufficiently comprehensive;
  - voluntary ex-post choice.
- database used if $t \in \{1, \varnothing\}$;
- 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'.*

2^{nd} 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 $t \in \{1, \varnothing\}$;
- optimal beliefs DM: sophisticated skepticism (Milgrom and Roberts (1986));
- $E\Pi_{No\_t} = E\Pi\left(q_x = 0\right)$;
- $\mathbb{K}_t^{VD} \equiv xqE\Pi\left(q_x = 1\right) + \left(1 - x\right) E\Pi\left(q_x = q\right) - \left(1 - x\left(1 - q\right)\right) E\Pi\left(q_x = 0\right)$;
- **Proposition 3** *If $K < \mathbb{K}_t^{VD}$, there exists a PBE in which the medical decision-maker extracts all the information from the firm.*

Voluntary Results Databases & Skepticism III

- $\mathbb{K}_t^{VD} > \mathbb{K}_t^{LF}$;
- **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 $K \in [\mathbb{K}_{No\_t}^{LF}, \mathbb{K}_t^{VD}]$;

Medical Decisions Based Only on Positive Clinical Trials

"...conclusions of therapeutic effectiveness based on a review of only the published trials may be seriously misleading"

Simes (1997), p. 134.

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.

3^{rd} Main Result

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

- Fully informed $=>$ voluntary results databases;
- Not able to be 'skeptical' $=>$ some qualified support for compulsory registries complemented through results databases.

Conclusions: 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;
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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;