Equipoise Lost: Ethics, Costs, and the Regulation of Cancer Clinical Research

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Jethro Hu
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Cancer Statistics...

- Leading cause of death for Americans < 85 years old
- Kills 23% of Americans
- Lifetime U.S. risk: Men = 44%; Women 37%
The Case for Regulation…

• Tuskegee syphilis study, 1932-1972

• Belmont Report, 1979
  Autonomy, beneficence, justice, fidelity, non-maleficence, veracity

• Vioxx fiasco
The Regulatory Traffic Jam…

- IRB, FDA, NCI, CTEP, CMMS, CLIA, DHHS, HIPAA, JCAHO, US Patent and Trademark Office
- 370-481 steps from concept to activation of a phase 2 or phase 3 cooperative group trial
- “Costly research Ferraris capable of reaching 200 mph... are permitted to go only 5 mph...”

How do you pick the Ferraris from the clunkers?
Has the Pendulum Swung Too Far?

- What has regulation gotten us?

  Toxic death rates on phase 1 trials:
  
<table>
<thead>
<tr>
<th>Year</th>
<th>Death Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1979</td>
<td>0.8%</td>
</tr>
<tr>
<td>2002</td>
<td>0.5%</td>
</tr>
</tbody>
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- If 30% (~$8000 per patient) of clinical trial costs are due to increased regulation,

- And increased regulation decreases the toxic death rate by 0.3%,

- And life-expectancy is 1 year

- then **cost per life-year saved is $2.7 million**
Consequences of Overregulation...

- **Higher costs**
  - $26,000 per patient and rising
    - 12.2% inflation-adjusted annual rate of increase from 1980-1990
  - $800 million to $2 billion per drug approved
  - ~2 full-time employees for a site to conduct trial of moderate intensity enrolling 20 patients
  - Time

- **Slower pace of research**
  - Focusing on ‘safety’ = no incentive to expedite research
  - Slower accrual
    - <5% of adult cancer patients participate in clinical trials
    - From 2000-2007, 40% of CTEP-sponsored trials met accrual objectives
  - Time from drug discovery to marketing:
    - 1960 8 years
    - Now 12-15 years
Overregulation = Lives lost?

- Advanced lung cancer example
  - *Assume* regulations have decreased the toxic death rate from 0.8% to 0.5%
  - *And* it takes an average of 5435 trial patients to get a drug approved
  - *And* life expectancy < 1 year
  - *Then* US regulations save **16.4 life-years**
  - *If* a therapy increases cure rate by 1%, and average life expectancy by 3 months
  - *And* regulations delay drug approval by **5 years**
  - *Then* **282,529 life-years are lost** as a result of this delay
  - *If* a therapy increases cure rate by 1%, and average life expectancy by 3 months
  - *And* regulations delay drug approval by **1 year**
  - *Then* **56,506 life-years are lost** as a result of this delay
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• Advanced lung cancer example
  - *If* a therapy increases cure rate by 1%, and average life expectancy by 3 months
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• Colonoscopy comparison
  - *If* colonoscopy saves 7951 life-years per 100,000 patients over 50
  - *And* there are 75 million people in US age 50 or older
  - *Then* colonoscopy saves 5.9 million life-years.
Overregulation = Lives lost?

Is saving a theoretical life ethically equivalent to preventing a toxic death?
Downstream Consequences...

- Only large pharmaceutical companies have the capital to drive the research agenda.

  Casualties:
  - Off-patent drug studies
  - Un-patent-able therapies
  - Combination therapies
  - Treatments for rare diseases
  - High-risk / high-reward research

- Less people interested in performing clinical research.

"You are completely free to carry out whatever research you want, so long as you come to these conclusions."
Proposed Solutions...

- Limit preclinical toxicology and pharmacology assessments
- Limit / centralize study review
- Simplify adverse event reporting / re-consent process
- Give investigators more flexibility
- Design better trials
Favorite Quote…

“It is just not all that important if it was day 5 versus day 6 that the patient’s grade 1 fatigue improved, particularly when the patient then dies on day 40 of uncontrolled cancer.”
Least Favorite Quote…

“Ayn Rand wrote, ‘The only power that any government has is to crack down on criminals... When there aren’t enough criminals, one makes them. One declares so many things to be a crime that it becomes impossible for men to live without breaking laws.’”

"He used to be into Buddha like the rest of us, but now he's into Ayn Rand."
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Is it possible to agree with this statement with regards to clinical trials, but disagree with it in other arenas?

(Can I rightfully decry overregulation in clinical trials, yet want more ‘rules’ imposed on bankers because I’m mad about the financial crisis?)
Concerns...

- Despite regulation, bad stuff happens.

- Our method of performing clinical research is flawed in several ways. Excess regulation is only one.
  - Focusing on ‘safety’ while ignoring ‘robustness’.
    - “The cult of p = 0.05”
    - Clinical trials are designed to look for small gains in a high proportion of patients, not large gains in distinct subpopulations.
    - No criteria for failure.
Thoughts?

“O.K., let's slowly lower in the grant money.”
"Can we, just for a moment, Your Honor, ignore the facts?"