Moral Principles or Expediency?

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Ethics and Legalities
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In my opening remarks I will briefly highlight the schism between ethical principles and the US regulatory system. A system that was established to safeguard human subjects by implementing those ethical principles.

Instead, the current system is geared toward lending the appearance of legitimacy to ethical expediency and corner-cutting at the expense of safety for the subjects of clinical trials and for consumers who are at increased risk of harm from defective drugs and devices. Vulnerable people who are poor, underprivileged, and in desperate need of medical care, are at greatest risk.

Ethical Research: A Collective Responsibility

"Unless researchers, gatekeepers and regulators incorporate the ethical principles outlined in codes such as the Declaration of Helsinki into their collective moral compass these codes will remain simply words."

Michael Goodyear, BMJ Editorial, Sept. 29, 2007

Ethical Research Principles

"The voluntary consent of the human subject is absolutely essential." *Nuremberg Code, 1947*

"considerations related to the well-being of the human subject should take precedence over the interests of science and society. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods." *Declaration of Helsinki, #5,29, 2000*

"Risks to subjects are minimized...procedures are consistent with sound research design which do not unnecessarily expose subjects to risk."

US Code Federal Regulations

Moral Principles or Expediency?

- Which standards govern research practice?
- Who determines if an experimental design is ethical / permissible?
- Who enforces ethics regulations?
- What penalties do violators face?
- Are Ethics Standards equitably applied?

If unenforced, what difference do regulations make

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Allure of the Poor

"While the average American brings home more than ten prescriptions a year, just one in 350 is willing to play guinea pig for new drug testing."

"Poor, under-treated, trusting patients in Eastern Europe, Latin America and Southeast Asia render the quick, positive results corporate sponsors need to get new drugs approved fast.
One study found a whopping 99% of controlled trials published in China reported positive results for the treatment under investigation."

Sonia Shah, The Body Hunters, 2006

Ethics for US Trials

Conduct of a placebo controlled surfactant trial for premature infants with RDS is considered unethical in the USA. The Division of Pulmonary and Allergy Drug

Ethics for Developing World

Internal FDA Documents

SCIENTIFIC ROUNDS
Presented by the Division of Pulmonary and Allergy Drug Products
January 24, 2001

Title: Use of Placebo-Controls in Life Threatening Diseases:
Is the Developing World the Answer?

Ethical Relativism Sacrifices Lives

B. ETHICAL ISSUES

respiratory distress syndrome

1. **Premature infants with RDS suffer a severe, life threatening illness for which they will not receive known, approved therapy that is SOC elsewhere in the world, and SOC even within other institutions in their own countries.**

2. **Infasurf gained marketing approval by demonstrating superiority over Exosurf, when placebo controlled trials in the US were no longer possible. A superiority trial versus Exosurf would leave no infant untreated.**

Ethics of "Financial Limitation" exploits the poverty of Latin American people and devalues their infants' lives.

FDA Documents

D. **The Sponsor has submitted a placebo-controlled Surfactant protocol in Latin American regions where other drugs in its class are approved, but not standard of care because of financial limitations or government rationing. Features of this protocol include the following:**

1. Multi-center, randomized, masked, two-arm study in 650 premature infants with RDS (325 patients per arm)

   placebo

2. Patients will be randomized to receive either Surfactant or "sham air", with otherwise identical study procedures.

3. Primary endpoint is all cause mortality at 28 days at age

Placebo Increases Probability of Death

In prior trials Surfactant reduced deaths by 34%

Cochrane Review, 2000

FDA estimate: in Latin America mortality rate among premature infants is 30%.
Of these deaths 50% due to
Respiratory Distress Syndrome.

+17 infants will die in placebo-controlled trial
(325 pts. X 0.3 X 0.5 X 0.34).

Public Citizen letter, Feb. 2001
http://www.citizen.org/publications/release.cfm?ID=6761

Whose Ethics Prevail?

1. Regulatory agency that approves sponsor's new product—FDA; EMEA?
2. Company seeking approval for new product?
3. International standards / practice—Helsinki, WHO, ICH-GCP, ICOMS?
4. Local ethics committees (IRB-REB)?
5. Community where trial is to be conducted?

Ethics of Corporate Expediency

B. A Surfactant superiority trial versus Exosurf in the USA and/or Europe is not considered feasible by the sponsor.

- Patient enrollment difficulties and "ethics" were cited as impediments to such a trial in developed countries.

Internal FDA Documents

Is globalization, a race to the ethical bottom?

Do Latin American infants' lives have no value?

FDA Ethical "Double Standard"

U.S. trained neonatologist teams will be sent to help ensure SOC comparability between Latin American and U.S. patients

Internal FDA Documents

US infants receive life-saving, standard of care (SOC) treatment —

Latin American infants do not!

"Comparability" ?

But for the Whistle Blower…

Surfaxin placebo-trial design was revised after an FDA scientist blew the whistle.

He alerted Public Citizen, a fellow consumer advocacy group, who filed public complaint.

“The Body Hunters”

2001: Washington Post documented a chilling array of abuses by academic / corporate researchers from prestigious US academic institutions—including Harvard, Johns Hopkins.

The experiments were conducted in Africa, Asia, China, Eastern Europe and Latin America. Abuses ranged from coercion, undisclosed risks, unapproved trials, denial of effective treatment, false promises of free medical treatment and other ‘benefits’ that never materialized.

Joe Stephens, Washington Post 2001

“A clear case of exploitation”

The Washington Post uncovered an “improper and unsafe” Pfizer experiment testing Trovan, an unapproved experimental antibiotic on 100 Nigerian children with meningitis.

The trial was conducted without informed consent—in violation of Nuremberg Code.

Eleven children died—others suffered brain damage, hearing loss, and paralysis.

Washington Post, 2000

Dubious Practices, US

1992-2001: Speculative experiment
exposed 68 children—some healthy—to risk by implanting a pacemaker at National Institute of Health.

Physicians complained at meetings and in medical journals that “the hypothesis about remodeling children's hearts was too radical to test on human subjects...“

Cardiologists scoffed:

“There's a lot of witchcraft here.”

Moss, Wall Street Journal, 1996

FDA Credibility Crisis

Institute of Medicine:

”Perception of crisis has compromised the credibility of the FDA and the pharmaceutical industry… [which] do not demonstrate accountability to the public.”

IOM. The Future of Drug Safety, 2006

Government Accountability Office:

“FDA lacks clear and effective processes for making decisions about safety.”

GAO. Drug Safety, 2006

Inspector General:

“FDA cannot identify the total number of clinical trial sites.”

OIG. FDA’s Oversight of Clinical Trials, 2007

“FDA Leadership, a Consistent Problem”

Cong. Hearing, 2007

Cost to Violators ?

2001: secret Nigerian Health Ministry report concluded that Pfizer had violated Nigerian law, the Declaration of Helsinki and the U.N. Convention on the Rights of the Child.

Washington Post, 2006

Trovan is banned in Europe. In the US its use is very restricted even for adults, due to liver toxicity and deaths.

*April 2009: 13 years after the illegal experiment...Pfizer settled civil & criminal lawsuits for $75 million.

A Modest Proposal

Absent moral leadership, absent any punitive remedies in current national or international research ethics standards,

The Alliance for Human Research Protection (AHRP) proposes:

1.Every sovereign nation should consider enacting punitive remedies in accordance with its own penal code against violators of ethical research principles.

2. FDA should not accept data from trials that violate US and / or local ethical standards.

1997: FDA reporting requirements for medical devices, rescinded.

"Distributors of medical devices are no longer required to report device related adverse events involving death, serious injury and malfunction to the FDA and /or the device manufacturer."

http://www.fda.gov/cdrh/devadvice/351.html

Loosened Regulatory Controls

Increased:

- dubious corporate practices
- # of defective devices approved
- # of devices recalled
- # of people killed and maimed

Defective Device Recalls

1,000 defective medical devices recalled annually in the U.S.

2002–2005: 4,475 defective device recalls

"despite the high cost to consumers… regardless of the severity of the device failure… shareholder losses do not dependably deter dubious firm practices

Product Recalls in the Medical Device Industry: An Econometric Analysis of the Costs of Poor Quality – Working Paper -January 2007

Dubious FDA Approval, VNS

2005: despite unproven efficacy

FDA approved Cyberonics' implantable electric shock device, Vagus Nerve Stimulation for depression.

>20 FDA scientists opposed VNS approval due to serious safety concerns including: cardiac risks, sudden deaths, suicides.

See: Sen. Grassley investigative report, 2006
*h*ttp://finance.senate.gov/press/Gpress/02_2006%20report.pdf

Dr. Daniel Schultz, Director, FDA Center for Devices, overruled safety team and approved VNS even without evidence of its effectiveness.

Two recent technology assessments by major insurance companies concluded:

> "*There is insufficient evidence to claim that VNS works to alleviate depression*." *Boodman, Washington Post, 2006*

Heart Rhythm Society Recommended

- Revised monitoring and publicizing system for implantable device performance problems.
- Improved recognition of potential device malfunctions in postmarket surveillance and reporting
- Improved communication among industry, federal agencies, clinicians and patients

2007: Johns Hopkins Hospital IRB waived consent requirements to test an intervention to decrease catheter-related bloodstream infections in patients hospitalized in Intensive Care Units.

See: US-Office of Human Research Protections l*etter of findings*: *http://www.hhs.gov/ohrp/detrm_letrs/YR07/jul07d.pdf*

The absence of regulatory enforcement encourages dubious research practices, hasty approval, and the marketing of harmful drugs and devices.