

Moral Principles or Expediency?

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Device Regulatory System:
Ethics and Legalities
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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?
3. Are Ethics Standards equitably applied?
 4. **Who enforces** ethics regulations?
 5. **What penalties** do violators face?

If unenforced, what difference do regulations make

?

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 renders 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”

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.

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

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

<http://www.washingtonpost.com/wp-yn/world/issues/bodyhunters/>

“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

10 years after the illegal experiment...
civil & criminal lawsuits

Trovan is currently not marketed in Europe. In the US its use in adults is very restricted due to its association with liver toxicity and deaths.

A Modest Proposal

Absent moral leadership by the US,
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.

Device Industry: Reduced Regulatory Controls

1997:

Reporting requirements 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

Increase:

dubious corporate practices

of defective devices approved

of devices recalled

of people killed and maimed

Dubious FDA Approval, VNS

2005: FDA approved Cyberonics' implantable electric shock device, Vagus Nerve Stimulation for depression—**despite unproven efficacy.**

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

See: Sen. Grassley investigative report, 2006

http://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*

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*

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

Absence of regulatory enforcement encourages dubious corporate practices and the marketing of harmful drugs and devices.

2007: Johns Hopkins doctors tested an Intervention to Decrease Catheter-Related Bloodstream Infections in patients hospitalized in Intensive Care Units **without informed consent**.

Hospital IRB had waived consent.

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