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Fundació Doctor Robert
UAB

ETHICAL ASPECTS OF HUMAN MEDICAL RESEARCH FROM A US/FDA PERSPECTIVE*

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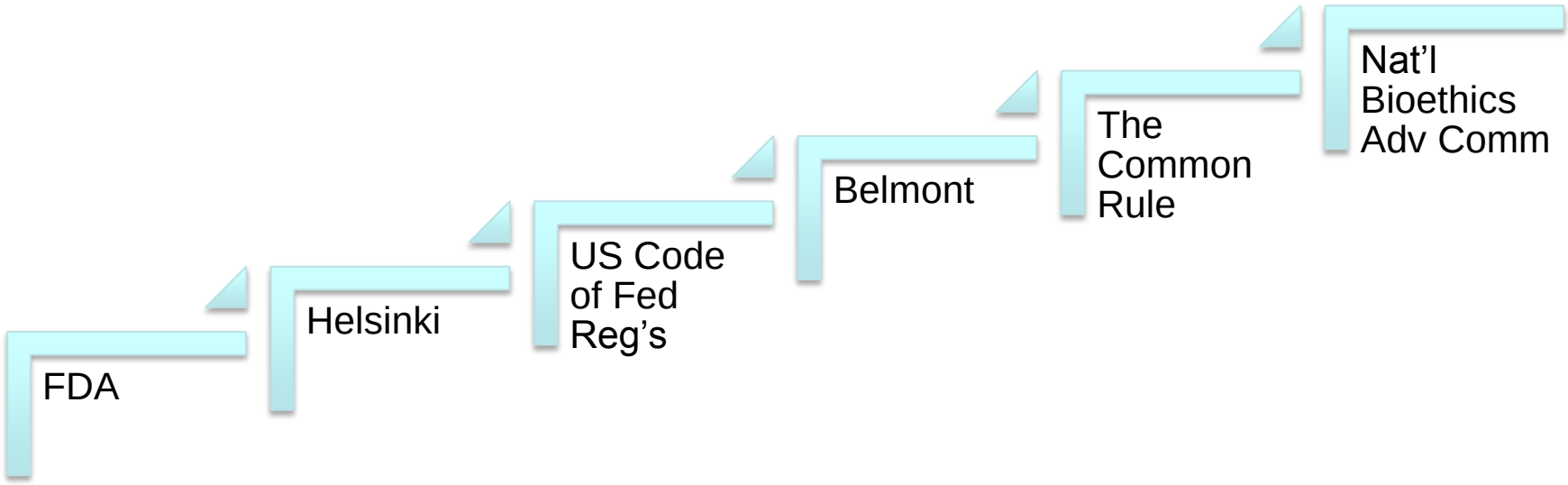
Early Regulations

- **1906 – Pure Food and Drug Act prohibited unsubstantiated claim on product labels**
- **1938 – Food, Drug and Cosmetic Act required proof of safety before product marketing**

A history of regulatory ethics



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Helsinki

- **Declaration of Helsinki - 2013**
- **http://www.wma.net/en/20activities/10ethics/10helsinki/index.html**
  - ONE ROLLING PAGE!
  - 3 sections
    - An introduction (2)
    - A list of principles (13)

      Risks, burdens and benefits (3)

      Vulnerable groups and individuals (2)

      Scientific requirements and research protocols (2)

      Research ethics committees (1)

      Privacy and confidentiality (1)

      Informed Consent (8)

      Placebo (1)

      Post-trial provision (1)

      Research registration, publication, dissemination (2)

      Unproven interventions in clinical practice (1)

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U.S. Code of Federal Regulations 1974 (*The Common Rule* 1991)

45 C.F.R. § 46 - Protection of Human Subjects

- Prior approval of research by **ethics committee**
- Written **informed consent** and documentation
  - **Is it understandable by the average patient?**
  - **Is it too simplified (four tablespoons of blood)?**
- **Equitable recruitment** of research participants
- Special protection for **vulnerable groups**
- Continuing review of approved research

The Belmont Report 1979

Ethical Principles and Guidelines for the Protection of Human Subjects of Research:

- **Respect for persons**
- **Beneficence**
- **Justice**

National Bioethics Advisory Commission (NBAC) 2001

Ethical and Policy Issues in **International Research: Clinical Trials in Developing Countries**

- Responsive to **local needs**
  - Can all cultures understand “clinical trial”?
- **Community involvement**
  - **Community Advisory Boards**
- **Placebo use only when justified**
- **Access to benefits**
- **Focus on informed consent**

Regulators (FDA) protect us

- Restrict, disqualify investigators
- Enforcement activities
- Warning letters
- Twitter, Flickr, Facebook
- International manufacturing inspection
- Priority “voucher” program
  - Novartis gets a malaria drug approved (neglected disease), they get a voucher for faster review of any future application they choose
- Presence on YouTube
- Conflicts of interest (bar too high?)

Social (digital) media violations?

- Of the **675 violations** examined during the years 2008-2012, 43 percent (n=290) involved digital media while 57 percent (n=385) involved traditional media.
  - The proportion and number of Warning Letters issued against digital media vehicles has declined every year since 2009.
- 5 FDA Warning letter areas (n in 2015)
  - Drug Promotion (4)
  - Compliance – alternative (6) letters, but multiple products
  - Manufacturing and product quality (6)
  - Scientific Investigation or Drug Security (0)

Safety, safety, safety

- **This modified 44-foot trailer is one of three units that make up FDA's chemistry mobile laboratory.**

The evidence of conditions that could make people ill are going to become the basis for action, rather than evidence of illness itself.

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www.clinicaltrials.gov

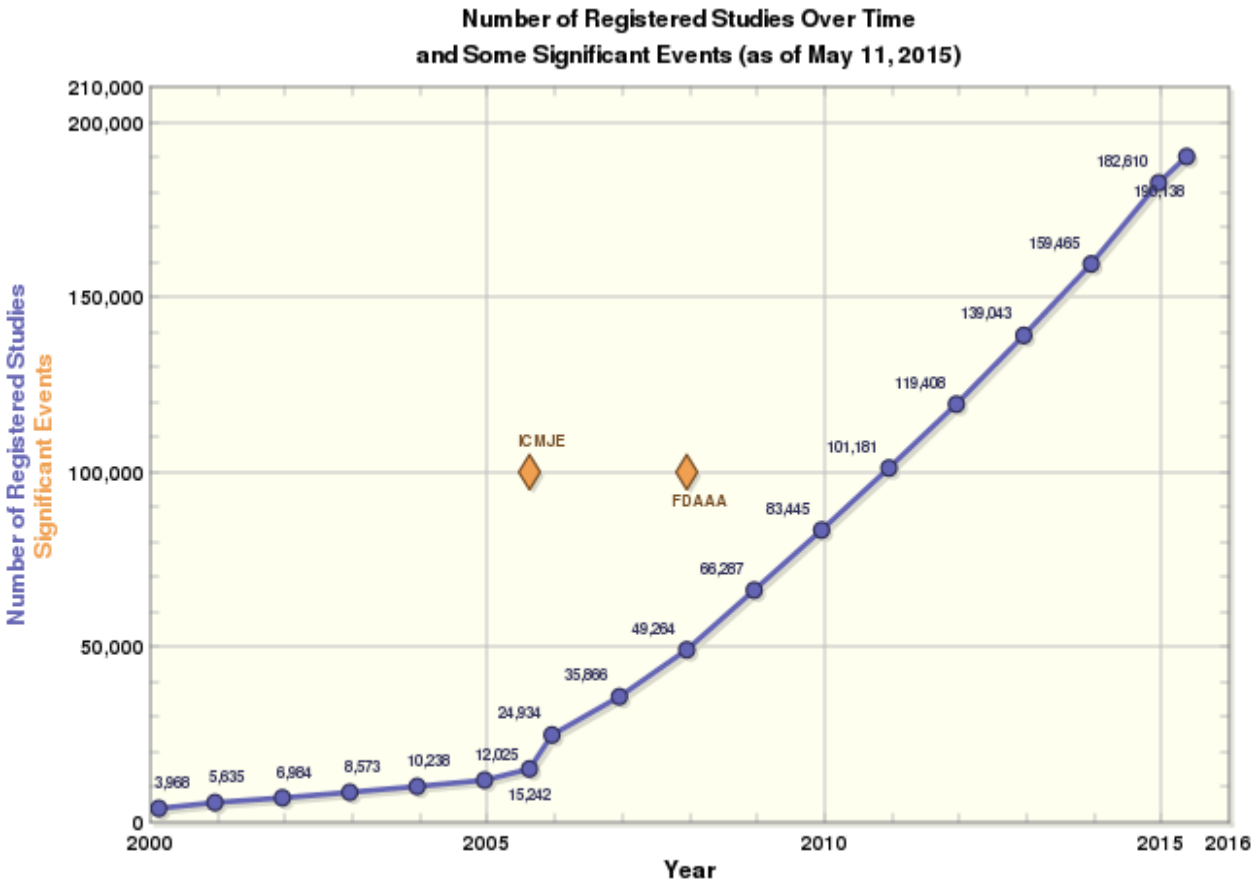
- **A registry** of clinical trials conducted around the world. ClinicalTrials.gov gives you information about a trial's purpose, who may participate, locations, and phone numbers for more details.
- **A Search Engine**

  Find trials for a specific medical condition or other criteria in the registry which currently has **190,138 trials in 190 countries** (**+13.5%** since last year). 57,000 unique visitors/day (112 million page views/month).
- **An Instructions manual**

  Get instructions for clinical trial investigators/sponsors about how to register trials.
- **Background**

  Learn about clinical trials and how to use ClinicalTrials.gov, or access other consumer health information from the US National Institutes of Health.

Clinicaltrials.gov registered studies



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Methods for approval

- **NDAs and BLAs** (10 months) and ***Priority*** **NDA and BLA** (6 months) – a major advance where no current therapy exists
  - Priority review voucher programs to reward pediatric inv/neg diseases, etc
- **Generic drug approvals**

- **Accelerated approvals**
  - S, LT with meaningful benefit over current therapies – usually, long-term diseases allowing surrogate markers (vs a clinical outcome like death)
- **FAST TRACK approvals**
  - Within 60 days for serious/life threatening conditions (UMN)
- **Cancer drugs**
  - Approval, accelerated approval
- ***Breakthrough*** **therapies**
  - Drugs with improvement over current therapies (S, LT)
  - All Fast Track features + more intensive guidance

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Safety, safety, safety

Drug alerts and statements

- Counterfeit drugs
- Undeclared ingredients
- Non-sterile ingredients

5 types of warning letters (promotion, compliance, manufacturing, scientific investigations, drug securtiy)

Safety, safety, safety

Monitoring patient safety during clinical trials

- to protect trial volunteers from preventable harm
- ongoing safety analyses during trials
- a causality assessment
- aggregate analyses (to reduce ‘noise’)
- ICH+
- serious, unexpected adverse reactions

- all this to increase the usefulness of safety data

Safety, safety, safety

- **Medwatch:** Consumer Voluntary Reporting
- Reporting
- Safety
- Staying informed

openFDA.gov/

- OpenFDA offers easy access to FDA public data and highlight projects using these data in both the public and private sector to further regulatory or scientific missions, educate the public, and save lives.
- In the future, openFDA will provide a platform for public challenges issued by the FDA and a place for the community to interact with each other and FDA domain experts with the goal of spurring innovation around FDA data.
- Currently focused on working on datasets in the following areas:
- **Adverse Events:** FDA's publically available drug adverse event reports, a database that contains millions of adverse event and medication error reports submitted to FDA covering all regulated drugs.
- **Recalls**: Enforcement Report and Product Recalls Data, containing information gathered from public notices about certain recalls of FDA-regulated products
- **Documentation**: Structured Product Labeling Data, containing detailed product label information on many FDA-regulated products
- FDA will be releasing a number of updates and additional datasets

Public Stakeholder Meetings

- **Patient network**
- **Webinars**
- **Patient newsletter, patient meetings**
- **Get informed, talk to FDA, Take action**

- **11 Public Meetings in June!**

FDA's budget

- **More on its plate – food contamination inspections; tobacco control**
  - 9 food recalls 2015 (2 salmonella, 2 undeclared milk, 1 listeria…)
  - 21 drugs week of 13 May (50% body building, beauty, 50% prescription drugs)
  - 9600 foreign food inspections

- **2015 budget increase presidential request of +9% - $4,744M** (€4.125M)

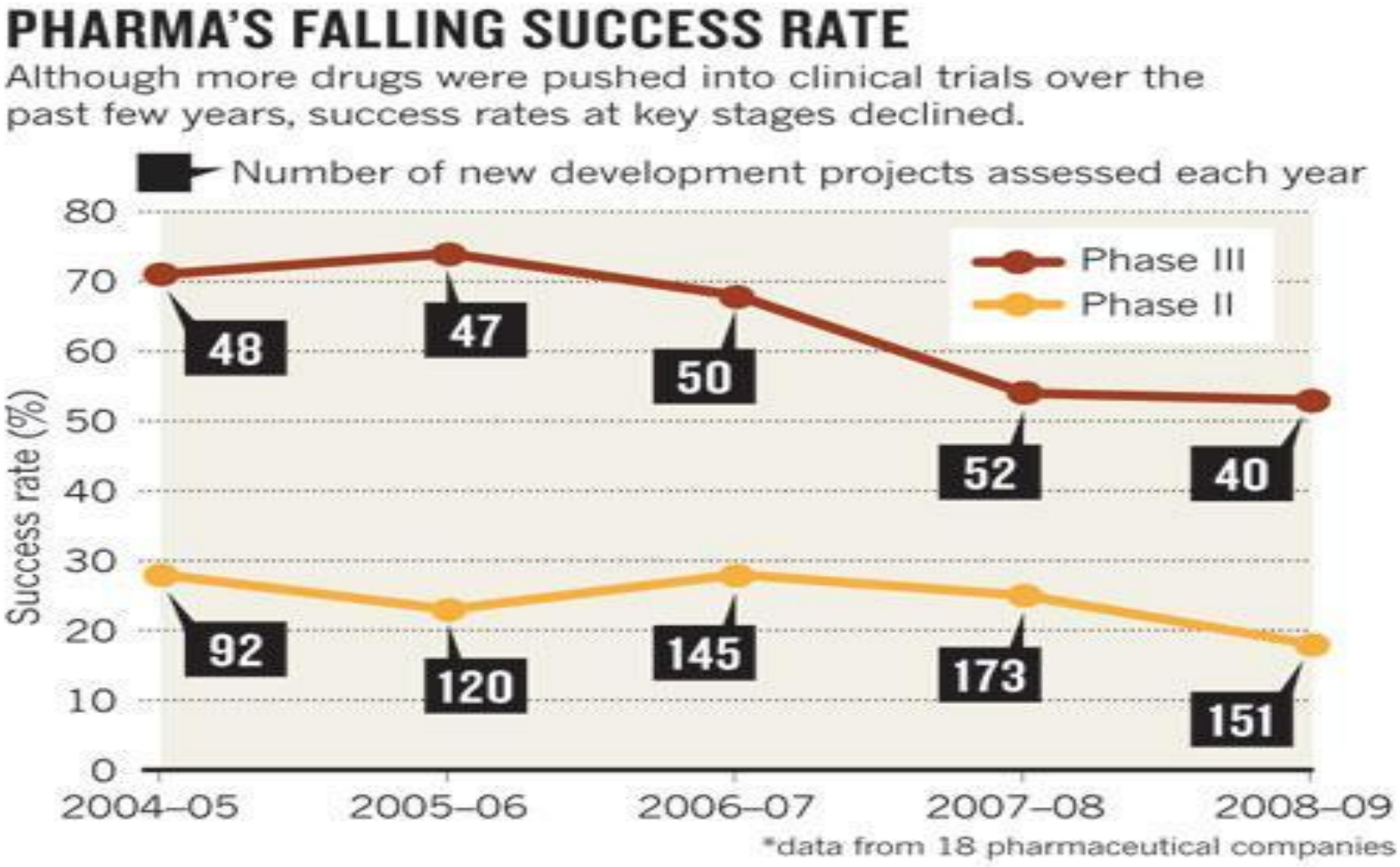
- **FDA globalization**
  - 10-15 percent of the U.S. food supply,
  - 50 percent of fresh fruits, 20 percent of vegetables, and 80 percent of seafood,
  - 40 percent of listed finished drugs, and
  - medical devices that constitute over 35 percent of the U.S. medical equipment market.

Backup slides

Bioethics debate

- **Does one principle take precedence over another?**
  - Should **Beneficence** be paramount, thus making it allowable to put people in research for their own good?
  - Should **Autonomy** trump all, making more risky research allowable if persons wish to participate?
  - Should **Justice** be the main focus and make attempts to correct for past injustices, or even force balanced demographics at the expense of other research questions?

Nature, 18 May 2011



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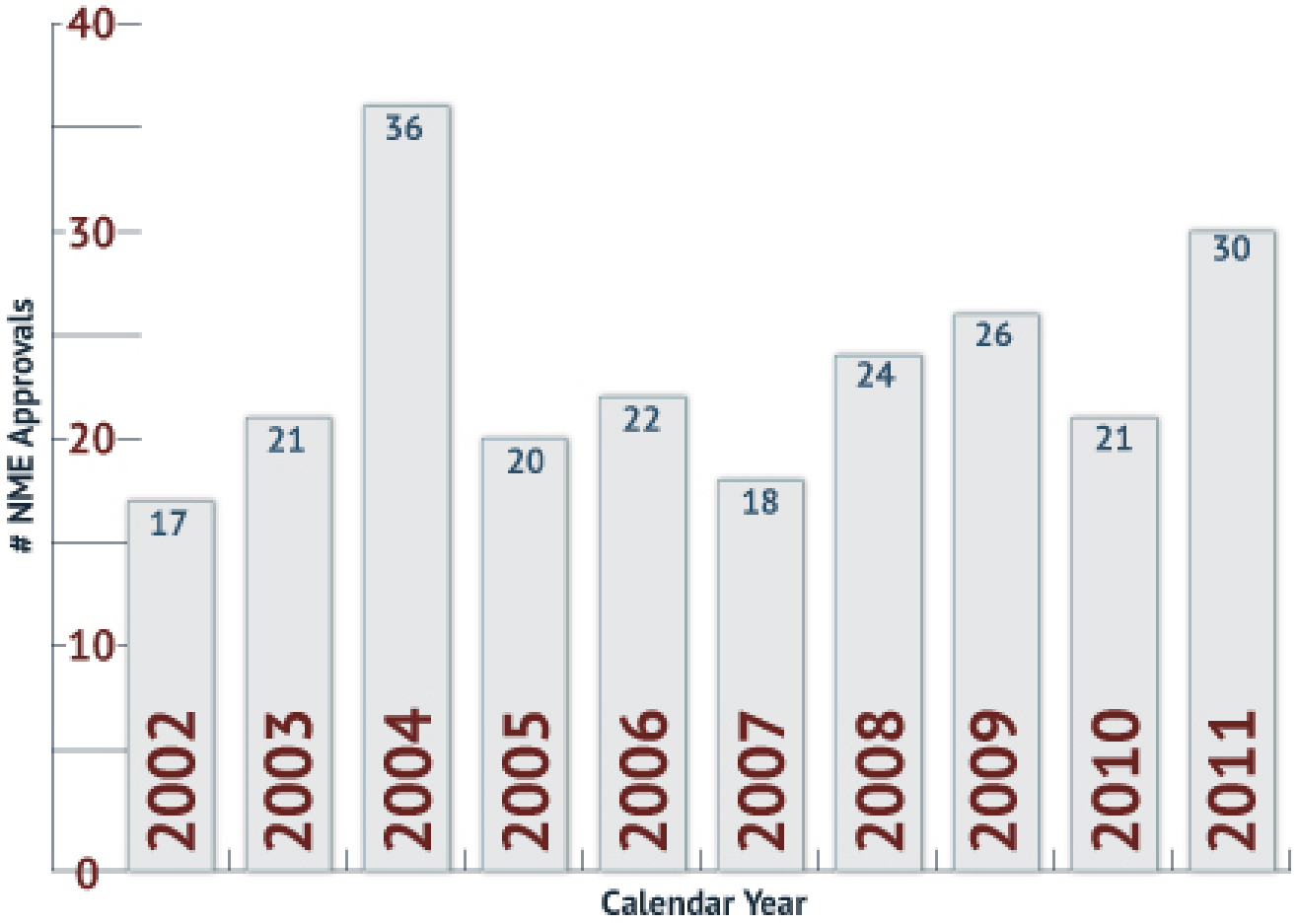
FDA-approved NMEs



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How expendable are ethics?

- **Trials must comply with the Declaration of Helsinki (or with local country laws, whichever offer the most protection) if sponsors want to use the data to win US marketing approval. The declaration, adopted in 1964, and revised several times since, is today endorsed by medical associations from 85 countries. It is widely considered to be the bedrock of protection for research subjects. It was most recently revised in S Korea in October 2008.**

Is ethics negotiable?

Good Clinical Practice (GCP) is modeled on a 1996 document developed by drug regulators and pharmaceutical industry representatives from the United States, the European Union and Japan.

- IRBs, Human Subject Protection (ie, Informed Consent), Safeguards for Children, Training & Outreach, International Harmonization.
- A clause of the 1964 Helsinki Declaration: "In research on man (sic), the interest of science and society should never take precedence over considerations related to the well-being of the subject". The new version of 2008 stands as: "In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests".

Clinical trials is a business

- **Payment should not be so high as to become an "undue inducement,"lest subjects enroll in risky, unpleasant, or degrading trials against their better judgment.**
- **The U.S. oversight system is not well equipped to monitor a highly competitive, market-based, multinational research industry. The Office for Human Research Protections has no jurisdiction over privately sponsored studies, and the Food and Drug Administration inspects only about 1% of clinical trials.[2] IRBs, the most important bodies charged with protecting subjects, review trial design, risk benefit ratios, and informed-consent documents. Recent research scandals which have been uncovered largely by investigative reporters rather than regulators have concerned a very different set of issues: fraud, conflicts of interest, unfair payment practices, and unsafe or degrading trial conditions. Such problems are magnified still further when studies are conducted at private testing sites and reviewed by for-profit IRBs that are financially dependent on research sponsors.**

Question 1

- **If the research offers a less effective treatment than available in the US but perhaps reflects all that is reasonable to be provided as Standard of Care in the setting, should the research proceed?**
  - what are current practices
  - what do you think
  - who should decide

Question 2

- **Individual Informed Consent**
  - should community/family consent be required by US funded research outside the US?
  - should anyone other than individual be allowed to consent for participants? should anyone else be informed of participation?
  - does community consent exist?
  - does the cultural protection of the foetus take precedence over the rights of the woman?

Question 3

- **Post-trial Benefits/Ancillary Care**
  - will the treatment or intervention be available to the participants or in the community following the research
  - will conducting the research in the community provide other benefits

is that a conflict

does it cause a research vs. clinical care confusion

is it coercion

Trial safety measures

- **2 year undercover investigation**
- **~10.000.000 people in trials every year**
  - Even with 10% poor or bad, that's 1.000.000 people in trouble!
  - Example: the GAO created a false company called Device Med-Systems, and submitted a made-up study protocol, signed by a made-up doctor, to Coast and two other IRBs. The protocol of the fake surgical product, Adhesiabloc, was based on a real product that the Food and Drug Administration (FDA) had withdrawn from the market because of adverse events.
  - Example 2: False IRB's can get registered!

Supply

- In 2010 there was a record number of drug shortages and in 2011 FDA has continued to see an increasing number of shortages, especially those involving older sterile injectable drugs.

- Manufacturers are not required to report information about shortages to FDA, and are not required to report the reasons for shortages or the expected duration of shortages on the FDA website.

- FDA encourages and appreciates all reporting of shortages by manufacturers.

  - **Fabrazyme (agalsidase beta); n = 71 (10.06.2011)**

    - **Manufacturing delays/issues; increased demand**