

International Research Compliance

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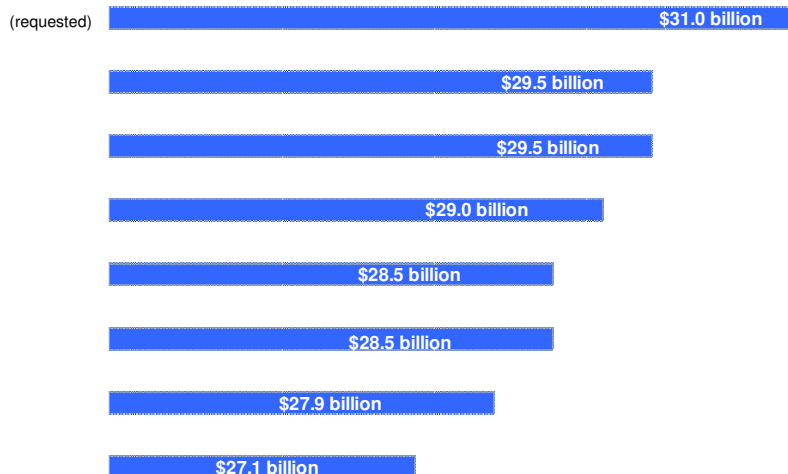
Dallas, Texas
April 2010

Objectives

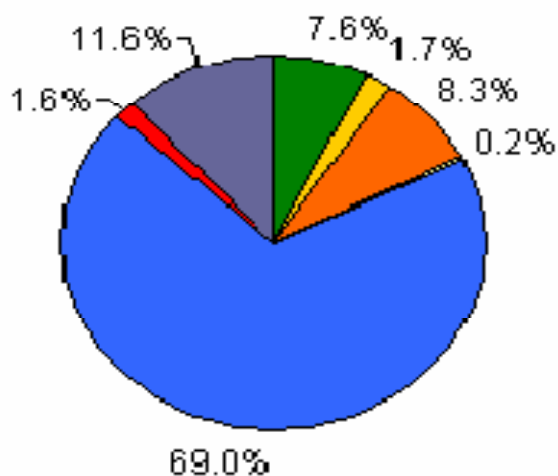
- US Perspectives, Funding & Inspections
 - OHRP
 - FDA
- Challenges
- Compliance

NIH Budgets 2003 - 2010

Plus \$10.4 billion provided by the stimulus package to be spent over the next 2 years



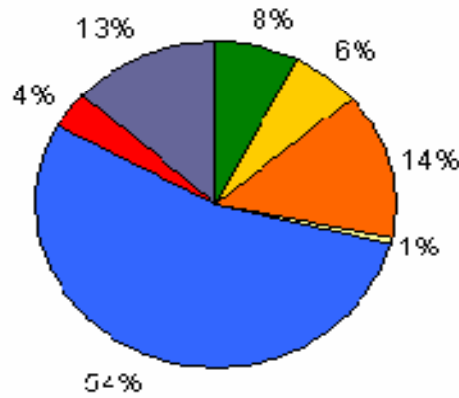
Extramural Research Dollars by World Region Average (FY 2004 - FY 2005)



N = \$597.916.000

Extramural Collaborators by World Region

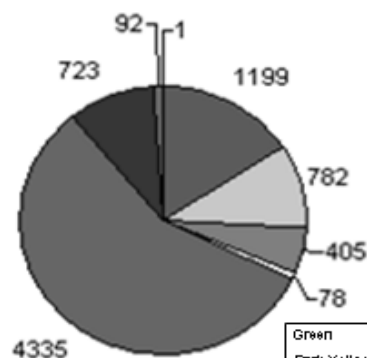
Average (FY 2004 - FY 2005)



N = 5,132 Extramural Collaborators



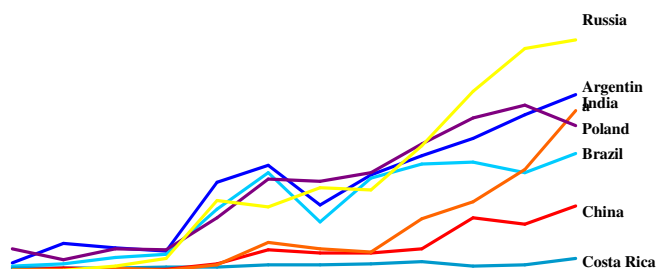
Number of Foreign Visiting Scientists on the NIH campus by World Region (Total FY2004-FY2005)



Top Ten Foreign Countries with NIH Research Funding Support in FY 2004 and 2005

| Country | FY 2004 | FY 2005 |
|----------------|---------------|---------------|
| United Kingdom | \$107,084,000 | \$98,042,000 |
| Canada | \$93,355,000 | \$86,629,000 |
| Denmark | \$85,971,000 | \$20,171,000 |
| Australia | \$46,259,000 | \$40,853,000 |
| South Africa | \$30,193,000 | \$32,722,000 |
| Thailand | \$18,130,000 | \$27,419,000 |
| Brazil | \$13,679,000 | \$18,386,000 |
| Sweden | \$15,471,000 | \$15,458,000 |
| China | \$11,545,000 | \$15,365,000 |
| Netherlands | \$9,139,000 | \$15,670,000 |
| Total | \$430,826,000 | \$370,715,000 |

Ex-US FDA Regulated Investigators



Source: Tufts CSDD Analysis of FDA's Bioresearch Monitoring Information System File (BMIS)

Regulatory Trends in Emerging Regions

FDA-Regulated Investigators 1996 vs. 2006 and 2004 vs. 2007

| | 2006 | % of Total | Annualized 10 yr GR | Annualized 3 yr GR |
|---------------------|--------------|--------------|---------------------|--------------------|
| N-America | 14,555 | 63.2 % | 1.8 % | -5.2% |
| W-Europe | 3,923 | 17.0 % | 7.5 % | -6.1% |
| CEE | 1,793 | 7.8 % | 41.4 % | 15.9% |
| L-America | 1,095 | 4.8 % | 27.3 % | 12.1% |
| Asia – Pac | 1,054 | 4.6 % | 25.6 % | 10.2% |
| ROW (ME/Afr) | 617 | 2.7 % | 11.0 % | 3.9% |
| TOTAL | 23,089 | | | |

Sources: Tufts Center for the Study of Drug Development / ACT Sept. 2007
CenterWatch Monthly, August 2008

Regulatory Trends in Emerging Regions

Growing % of patients are from Emerging Regions

| Region | % of total patients enrolled in trials in 2007 ** |
|---------------------|--|
| Traditional* | 58% |
| Emerging | 42% |

* USA, Canada, W.Europe

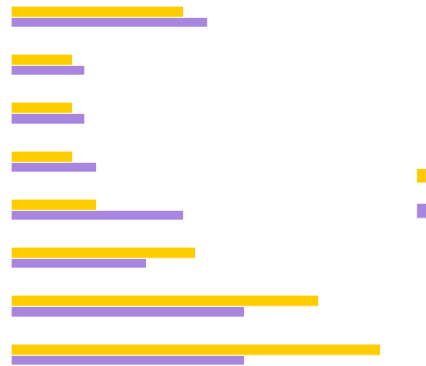
** Methodology: based on FDA 1572 investigators in regions

Regulatory Trends in Emerging Regions

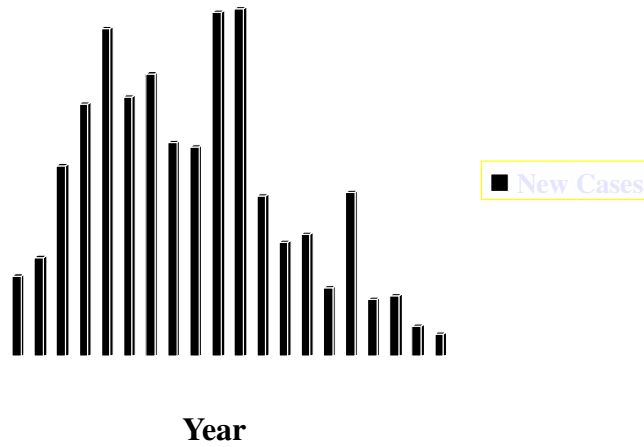
FDA inspections 2006 – 2008:

- USA: 30 OAIs/557 inspections = 5.4% OAIs.
- Ex-USA: 1 OAI/187 inspections = 0.5% OAIs.

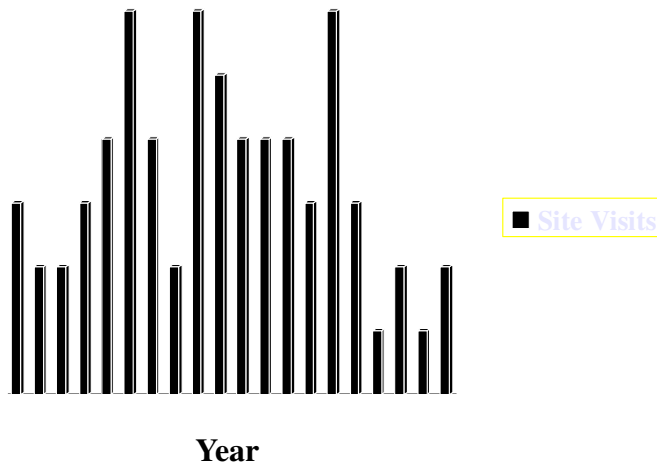
Geographical Distribution of Clinical Trials



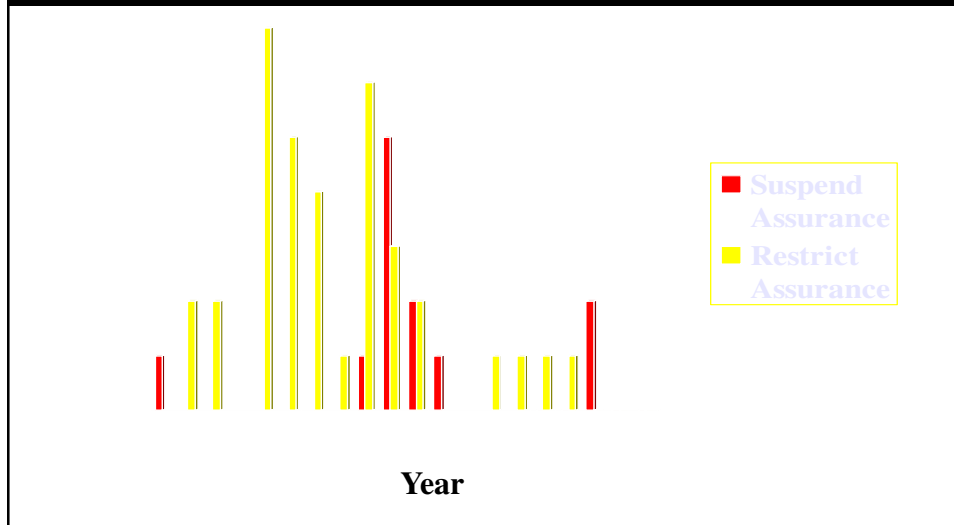
OHRP Compliance Oversight Activities New Cases Initiated – 1990-2008



OHRP Compliance Oversight Activities Site Visits – 1990-2008



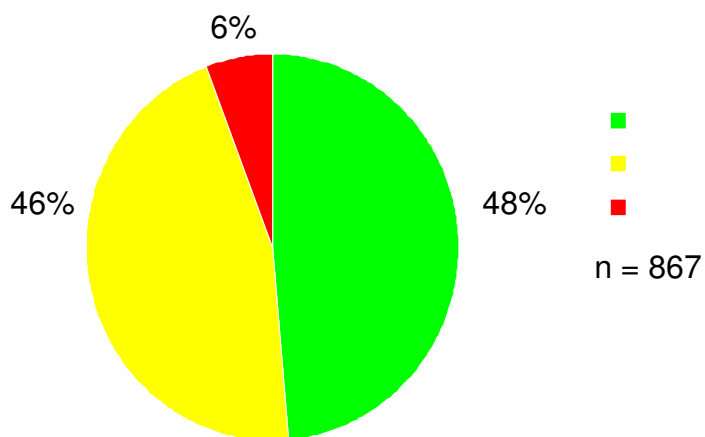
OHRP Compliance Oversight Activities Suspend/Restrict Assurance – 1990-2008



BIMO Inspections (2009)

| <u>Center</u> | <u>CI</u> | <u>IRB</u> | <u>Spon/Mon</u> | <u>GLP</u> | <u>Total</u> |
|--------------------|-----------|------------|-----------------|------------|--------------|
| CBER | 83 | 15 | 11 | 6 | 115 |
| CDER* | 458 | 102 | 73 | 36 | 669 |
| CDRH | 163 | 79 | 59 | 4 | 305 |
| CFSAN | 0 | 0 | 0 | 1 | 1 |
| CVM | 26 | na | 4 | 15 | 45 |
| All Centers | 730 | 196 | 147 | 53 | 1135 |

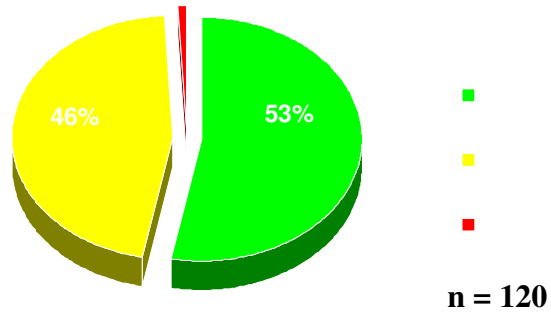
FY'09 CI Inspections - All Centers



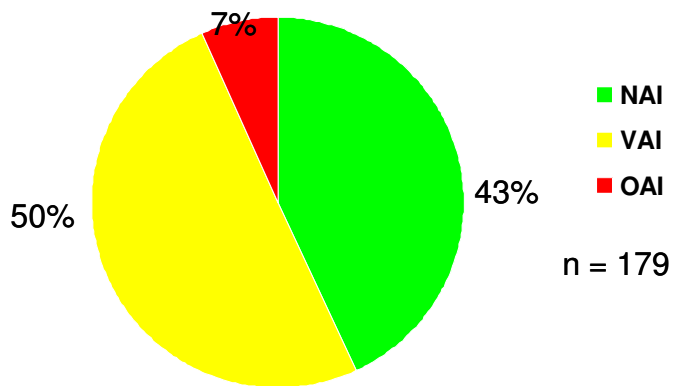
International Inspections (2009)

| <u>Center</u> | <u>Total</u> |
|---------------|--------------------|
| CBER | 2 CI + 1 Sponsor |
| CDER | 119 |
| CDRH | 10 CI + 2 Sponsors |
| CVM | 0 |
| Totals | 134 |

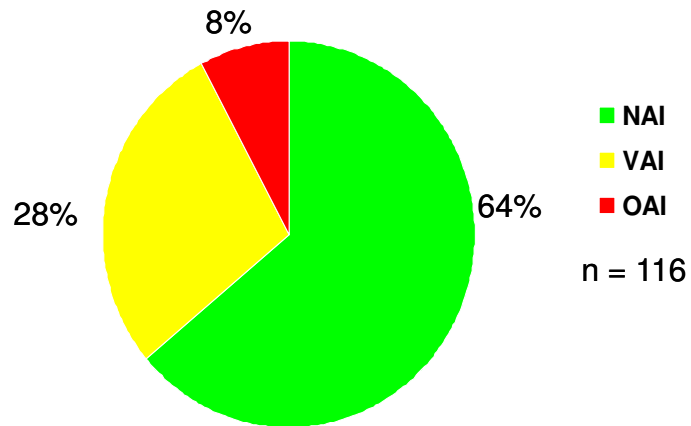
CDER CI International Inspections (2009)



FY'09 IRB Inspections – All Centers



FY'09 Sponsor/Monitor Inspections – All Centers



Challenges in Clinical Trials

- Conducted outside of academic centers
- Multisite trials
- Overseas/EX-US trials/sites

Challenges in Clinical Trials

- Increase IRBs' responsibilities
 - Ethical review of research
 - Management of conflicts of interest
 - Privacy
 - Risk management
- IRB Burdens
 - Limited resources

Challenges in Clinical Trials

- Subject/Patient
 - Wants access to investigational products
 - Concerned about adequate protection for human subjects

Challenges in Clinical Trials

Congress/Media/Public Interest in:

- Investigators' financial ties to sponsors and products
- Adequacy of FDA oversight of CI responsibilities and trial conduct
- Adequacy of IRB oversight
- Safety of trial participants
- Adverse events and clinical trial results

International Research Compliance

- Shared Responsibilities
 - Institution
 - IRB
 - Investigator
 - Sponsor, CRO
 - Regulatory Agencies

Institutional Official

“The Buck Stops Here”

- Institutional authority
- Sets “tone”
- Knowledgeable contact for OPRR

Institutional Official

- Appoint IRB members
- Provide resources and staff
- Support IRB decisions
- Ensure institution-wide communications
- Encourage educational activities

IRB Chair Responsibilities

- IRB functions
- Expedited review
- Reporting (to IO)
- Education

IRB Responsibilities

- Prospective review of research
- Continuing review of research
- Require informed consent
- Require I.C. documentation

IRB Responsibilities

- Notify investigator
- Authority to suspend or terminate research

IRB

- Knowledge required
 - Ethical principles
 - Federal regulations
 - State laws
 - Assurance
 - SOPs (or institutional policies & procedures)

IRB

- Familiarity with:
 - Subject populations
 - Institutional constraints
 - Legal requirements
 - Other factors

Investigator

Primary responsibility for protecting human research subjects and complying with assurances

Investigator

- Complies with IRB determinations
- Ensures subject comprehension

Investigator

- Provides subject with consent document
- Retains signed consents

Investigator

- Requests IRB approval of proposed changes
- May eliminate immediate hazards to subject and follow-up with IRB

Investigator

- Reports progress to IRB
- Reports unanticipated
- Injuries or problems to IRB

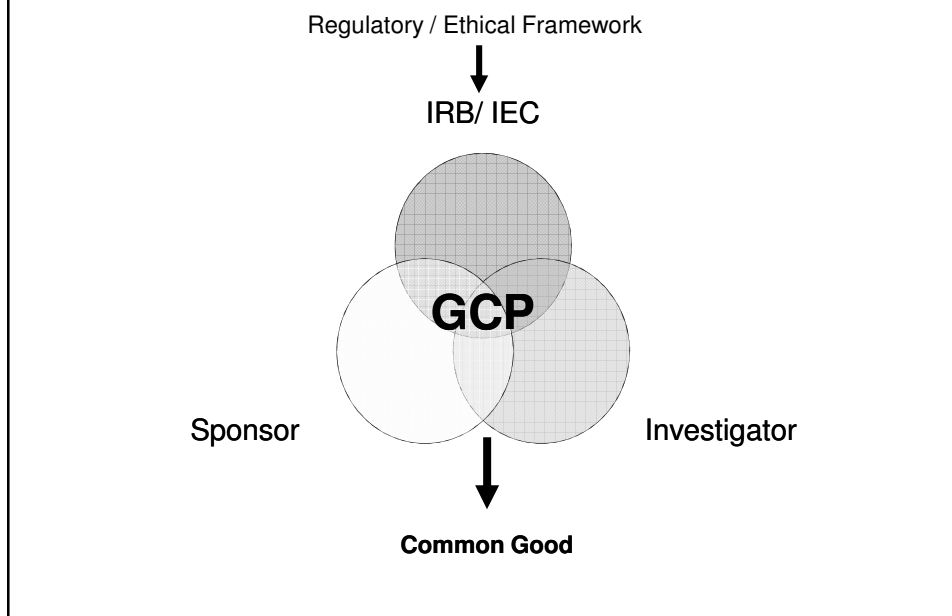
Sponsor Responsibilities

- Implement/maintain QA, QC system with SOP
- Ensure direct access to source documents from all parties
- QC should be applied to each stage of data handling
- Ensure agreements are written with PI and CRO

Contract Research Organization (CRO)

- Specified in writing any task assumed by a CRO
- Sponsor is ultimately responsible for quality and integrity of data
- References to sponsor also apply to CRO

Shared Responsibilities



Foreign Data

New FDA Requirement (April 2008)

- 21 CFR 314.106 Foreign Data
 - A) Acceptance of foreign data
 - Foreign clinical studies not conducted under an IND. Must submit in an NDA documentation on:
 - Qualification of investigators
 - Description of research facilities
 - Protocol, Clinical Study Report, Case Report Forms as requested
 - Chemistry, Manufacturing and Controls information
 - The study is adequate and well controlled
 - The study conforms with ethical principles

Foreign Data

- 21 CFR 314.106 Foreign Data
 - B) Can be the sole basis for approval
 - Foreign data are applicable to the U.S. population
 - Studies have been performed by Competent investigators
 - FDA can validate the data (inspection)
 - C) Applicants are encouraged to meet with the agency

Foreign Data

Regulatory acceptance of clinical data

- International Conference of Harmonization
 - E5 Ethnic Factors in the acceptability of foreign clinical data
 - ICH guidelines are adopted in three regions
 - European Union, Japan and the U.S.
 - Widely recognized by other authorities

Practical Issues

- Risk insurance
- Visas
- Intellectual property/ownership of deliverables
- Human subjects protections
- Budgets
- Communications

Risk Insurance

- Insurance
 - Worker's compensation insurance (institution)
 - Medical insurance (individual)
 - Emergency evacuation insurance (institution)
 - Institution's liability insurance
 - Local insurance requirement (property, fire, health for local employees/local human subjects)?

Visas

- Requirements differ from country to country – embassies have information
 - Check “entry/exit requirements” for the specific country on the U.S. Dept of State website:
<http://travel.state.gov/trave/cis.pa.tw/cis/cis1765.html>
- Costs of obtaining a visa may be charged to a sponsored project

Intellectual property (IP)

- US Patent law vests ownership of IP to inventor-foreign patent laws may not have similar protections
- Foreign corporations/entities are generally unfamiliar with US university position on retention of ownership of IP - there is a significant learning curve in the negotiation

IP

- Some issues with international collaborators on intellectual property ownership
 - Background IP
 - Patent costs
 - Publishing results of research/foreign patents
 - First to invest (US) vs. First to File (most foreign)
 - Publishing can jeopardize foreign patents
 - Marketing pre-patentable information (export issues)
 - Joint ownership of IP
 - Sounds good – but watch out for tax and legal presence
 - Foreign taxes on royalties of inventions created overseas

Human Subjects Protections

- Subrecipient engaged in the human subject research?
- IRB reviews
 - Federal funding requires that foreign organizations engaged in human research comply with U.S. regulations and have a Federal-Wide Assurance with OHRP
 - Frequency of review and reporting
- IRB's standard and policies
- Cultural sensitivities

Budgets

- Most international trials should consider:
 - Foreign travel
 - Shipping and communication
 - Translation services
 - Audit
 - Administrative oversight/fee (as a direct cost to the sponsored project)

Budgets

- For projects performed by institution at foreign sites, also consider:
 - Insurance
 - Visa costs
 - Expatriate allowances and benefits
 - Security
 - Local site employee
 - Customs duties & local taxes

Communications

- Time zone difference
 - When it is 9:am in Washington DC it is 9:pm in Asia
 - Achieve in depth conversation with foreign organizations?
- Language Difference
 - The PI generally speaks English, but the administrators do not.
 - Assured that administrative issues are understood and addressed?

Thank You!

