Globalization of Clinical Trials
Promise and Reality

Zvi Ladin, Ph.D.

Boston MedTech Advisors

www.bmtadvisors.com

November 2008

Outline

- Ethical principles
- Historical perspective
- Registration requirements
- FDA acceptance of foreign clinical data
- Global trends in conduct of clinical trials
- Global opportunities
- Global challenges

Ethics (or Example #1)

- New ‘block buster’ drug being developed
  - BIG profits?
- Need to quickly test it
- Some questions regarding side effects
  - Could be serious
  - Need large number of patients for testing
  - Too costly (and too risky?) to study in developed countries
- Solution
  - Go to Africa
  - Paint as ‘humanitarian effort’
- Voilà – a ‘blockbuster’ movie

Historical Infamy (or Example #2)

- Tuskegee Syphilis Study
  (1930s – 1972)
  - 399 black men signed with the US PHS for free medical service
  - Men were told they had ‘bad blood’
  - Disease followed without treatment
  - Penicillin – available since 1947
  - Outcome:
    - 28 men had died of syphilis
    - 100 others were dead of related complications
    - At least 40 wives had been infected
    - 19 children had contracted the disease at birth
  - Presidential apology (Clinton) – 1997


(Courtesy National Archives)

(CNN)

Protection and Improvement of Public Health

Information Supply

- Clear new drugs / technologies expeditiously
  - Quick studies
    - Limited populations
    - Limited duration
  - Limited Information
    - Adverse events (severity, incidence)

Information Demand

- Treat large populations
  - Adverse events
    - Low incidence
    - High severity
    - Lead to….
  - Complications
  - Public outcry

Developing a Legal Framework

- 1947 – Nuremberg Code
- 1964 – Declaration of Helsinki adopted – World Medical Assoc

USA

- 1966, NEJM – Henry Beecher, MD
- 1960's – Patient consent – FDC
- 1970's – IRB review of clinical protocols
  - 1972 – NIH established OPRR (Office for Protection from Research Risks)
  - Risks and benefits of research
- 1981 – FDA requires written patient consent

Europe

- Maurice Pappworth, MD
  - 1967 – Human Guinea Pigs
- 1960's – Patient consent
- 1970's – MDD
- Competent Authorities
- Notified Bodies

1998 Office of Inspector General (OIG) Report – Clinical Research's Shifting Environment

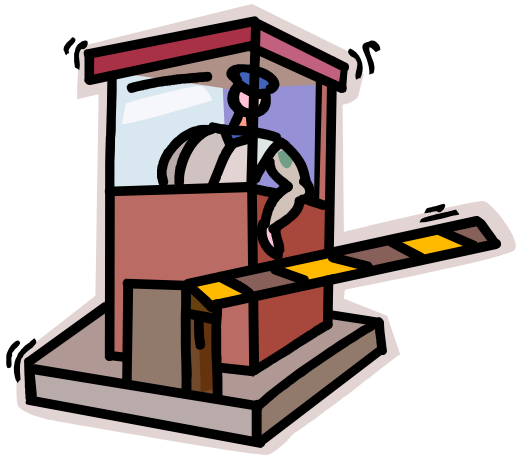
- Funding – from public to private
  - NIH ⟶ industry
- Nature – from single site to multi-center
  - Limited information to local IRB
- Size and numbers

1998 OIG Report – Revamping the IRB

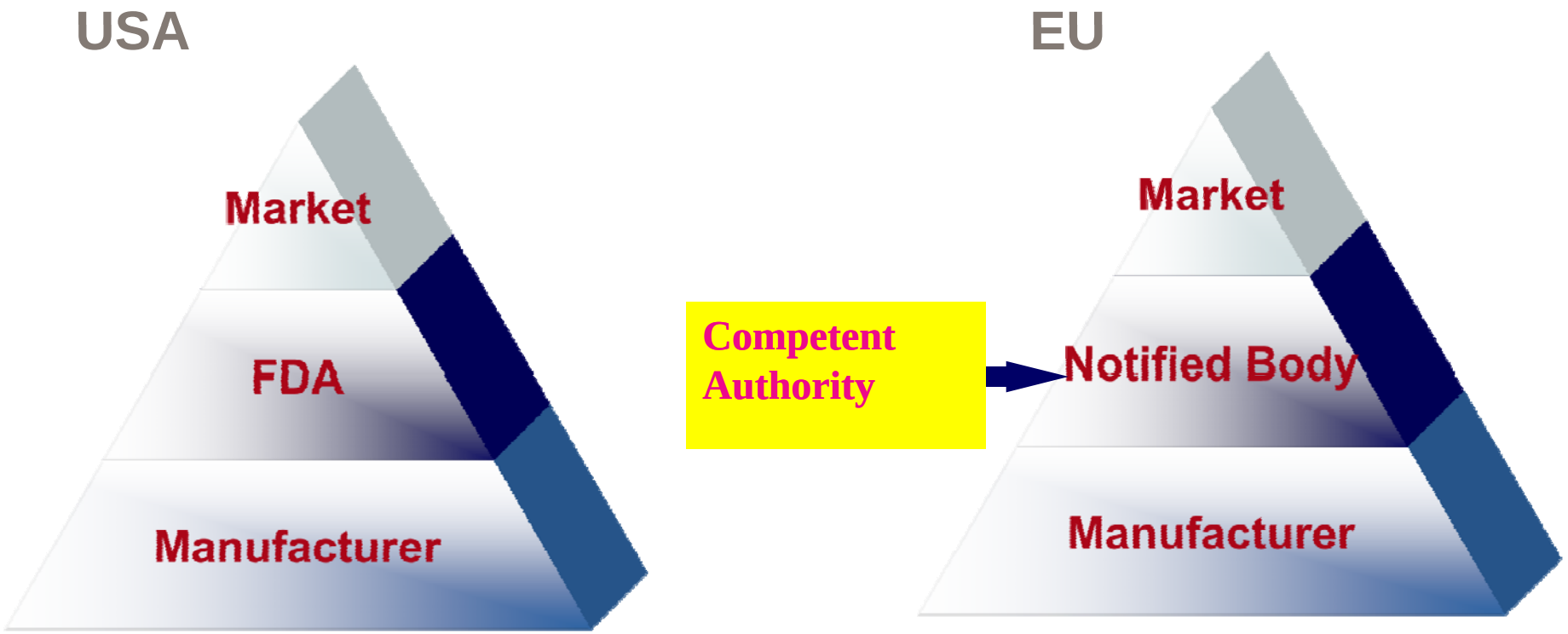
- Overwhelmed Local IRB
  - Time and expertise limiting review
  - New ethical issues (e.g. genetic screening)
- Evaluating IRB Effectiveness
- Conflict of Interest Inside the IRB
  - Part of the organization that gains from research
- Limited Training of IRB Members and Researchers

Understanding the Regulator

- Global ethical / legal framework
  - Nuremberg trials
  - Helsinki Declaration
- Local implementation
  - Culture
  - Language
  - Infrastructure
  - Economic pressures



Regulatory Interactions



Global Trends in Clinical Trials Conduct

Observation (Cause?)

- 1980's – increased regulation in US (FDA)
  - FDA acceptance of European clinical data
- European Union Clinical Trial Directive (2001)

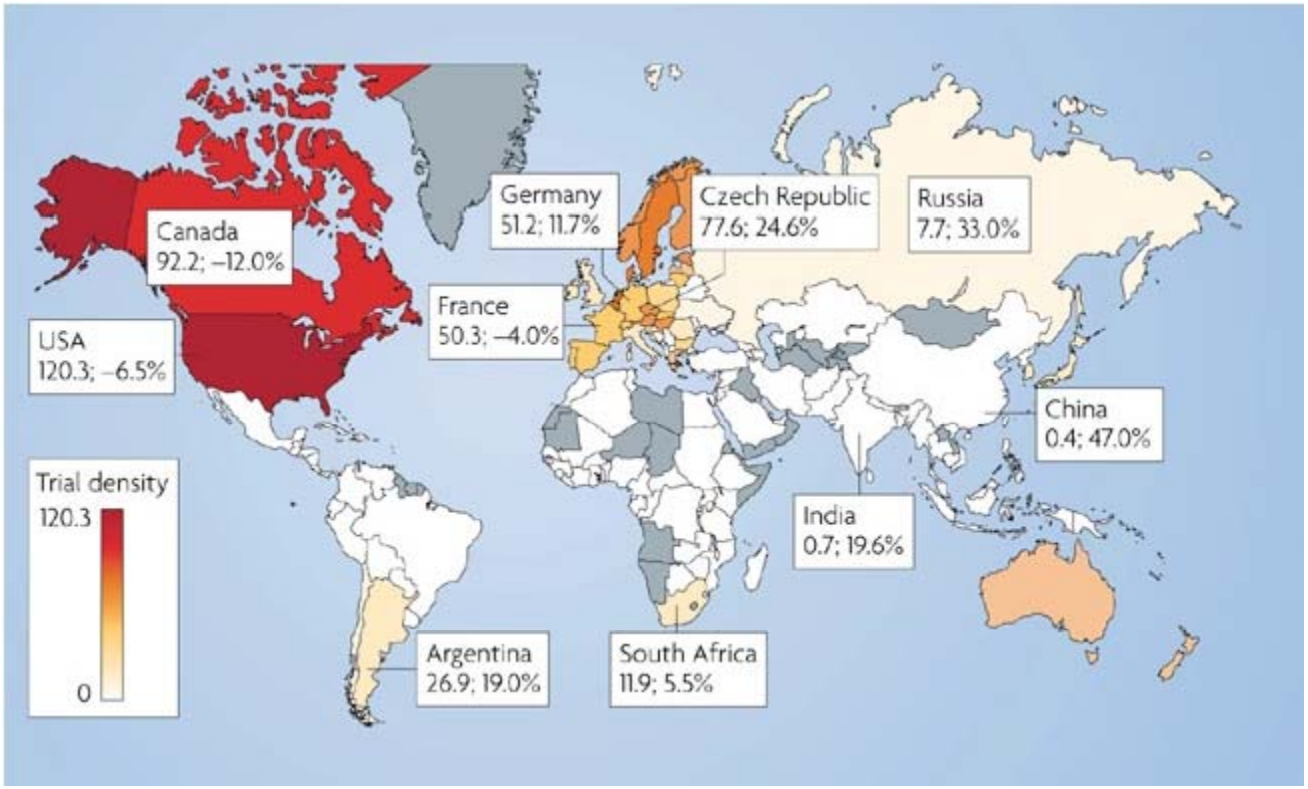
Observation (Effect?)

- Migration of clinical trials to Europe
- Migration of clinical trials to India, Russia and China

- Tassignon JP. The globalization of clinical trials. Applied Clinical Trials (2006)

ClinicalTrials.gov:

- >36,000 sites (through 1/'07)
- 140 countries

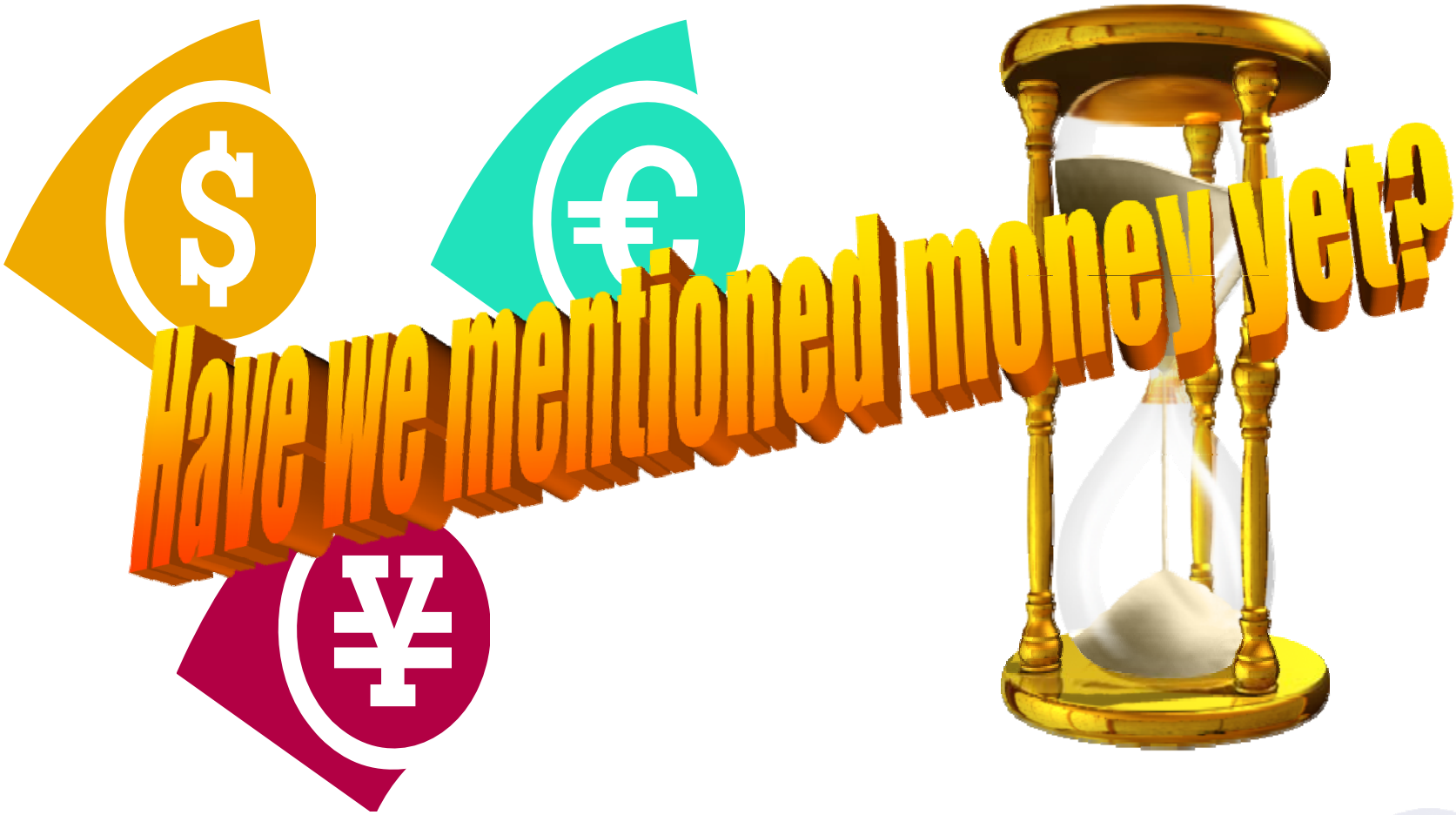


Ref: Trends in the globalization of clinical trials, Fabio A. Thiers, Anthony J. Sinskey & Ernst R. Berndt
Nature Reviews Drug Discovery 7, 13-14 (January 2008)

New Opportunities – Latin America

- Streamlined laws make Latin America attractive to sponsors
- October 2008 – 20% growth in the number of international clinical trials over four years

Country	Open Trials
Brazil	323
Mexico	292
Colombia	107


Have we mentioned money yet?

Economic Drivers

Increase regulation

- Increase
  - Costs
    - Investigators
    - Clinical environment
    - Monitors
    - Patient recruitment
  - Time
    - Longer
  - Effort
    - Higher

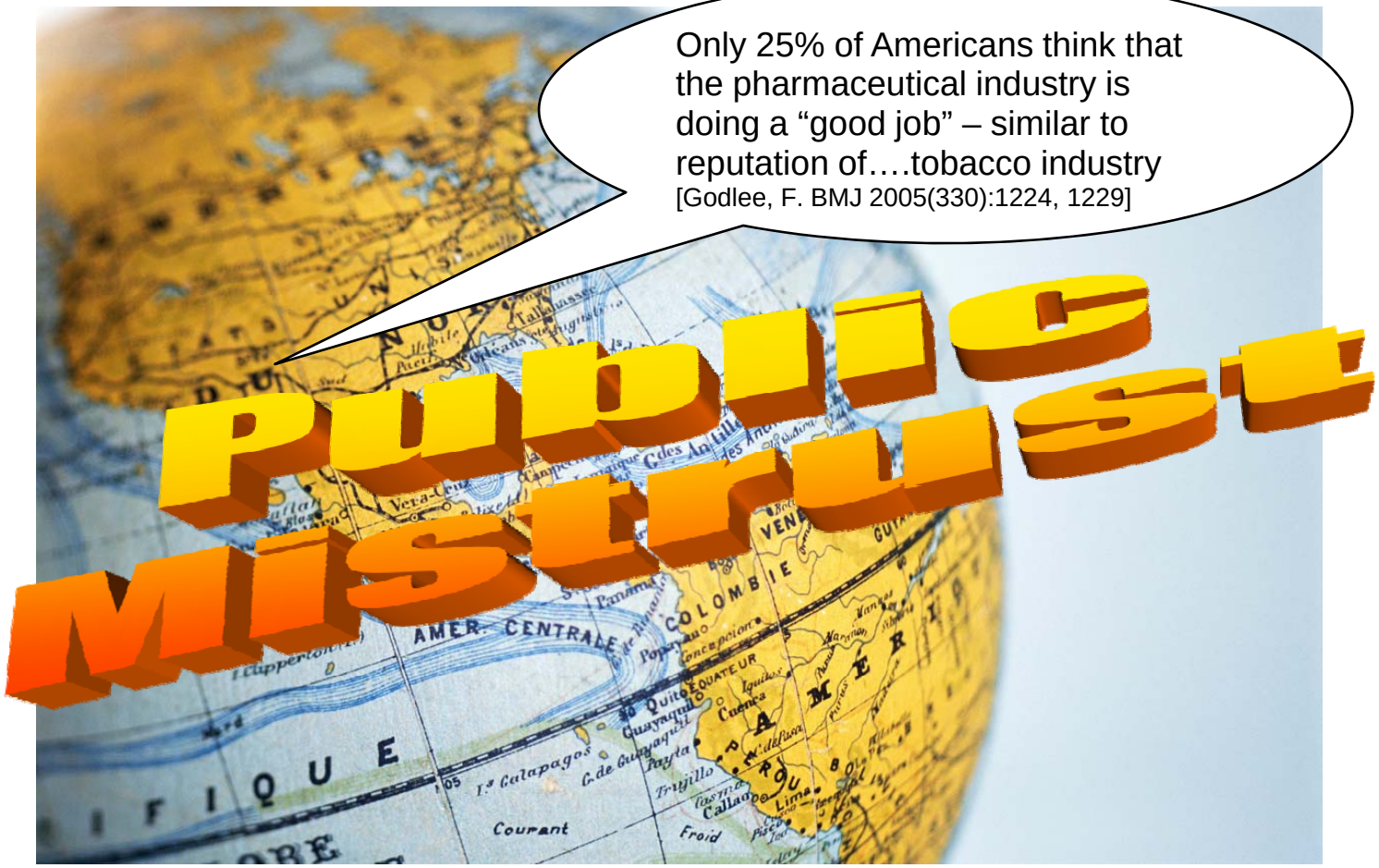
Move studies to:

- Less regulated countries
  - Time
    - Faster study initiation
    - Lower regulatory overhead
- Less expensive cost of living
  - Lower costs
- **However…..**

2004 – Clinical Trial Outcry (or Example #3)

- GlaxoSmithKline (GSK) Paroxetine treatment of depression in children
  - Attorney General of NY sued company
  - Allegation
    - Company selectively published positive partial results
    - Off-label promotion of drug by company
  - Settlement
    - GSK published all study results on Web
- 150 Scientists and organizations signed the Ottawa statement
  - Mandatory trial registration
- International Committee of Medical Journal Editors (ICJME) of 12 leading medical journals – no publication of unregistered studies
- Ministerial Summit on Health Research in Mexico
  - WHO
  - 52 Countries

Global Goals



Restoring Public Trust

Patient

- Full disclosure
  - Procedure
  - Alternatives
  - Risk / Benefits
  - Beneficiaries
    - Financial interests

Regulators

- Study approval
  - National regulatory authority
  - Local committee
    - IRB
    - Helsinki committee
- Complete and comprehensive information submittal
  - Related studies
  - Device safety

Community

- Clinical
  - Disclosure
  - Conferences
  - Publications
- Public
  - Registries
  - Patient groups

Clinical Trial Registration

- US FDA requirement – ClinicalTrials.gov
  - Established under FDAMA (1997)
    - First version – February 29, 2000
    - Initially mandated for only drug treatment of life threatening diseases
    - Expanded to include all trials conducted in US
    - October 2003 – 1000th study registered
    - Registration for non-life threatening treatments – RECOMMENDED!
- WHO International Registry
  - Established 2004
- Enforcement
  - FDA (limited to life-threatening treatments)
  - WHO (none)

Date	US Registration	WHO Registration
2003 (October)	1000	0
2004	13,000	0
2006 (June)	>40,000	12,000

WHO Clinical Trial Registry

- http://www.who.int/ictrp/en/
- Major components of trial including:
  - Contact information
  - Sponsor / source of support
  - Countries
  - Interventions
  - Key inclusion / exclusion criteria
  - Study type
  - Sample size
  - Recruitment status
  - Outcomes
- No requirement to report results

FDA Acceptance of Foreign Data (IND)

- Final Rule Published (effective October 27, 2008)
- 21 CFR Part 312
  - Non-IND foreign clinical studies
- Previous Requirement
  - Adherence to ethical principles stated in 1989 Helsinki Declaration (World Medical Association)
- Current Requirement – GCP
  - Includes review and approval by independent ethical committee (IEC)
  - Non-compliant studies
    - Have to be submitted
    - Cannot be accepted as support

FDA Acceptance of Foreign Data (PMA)

- 21 Section 814.15 (last amended December 2, 1986)
  - Valid data
  - Conformance with Helsinki Declaration or local laws and regulations
    - Whichever accords greater protection to the human subjects
  - If data is sole basis for submission:
    - Data applicable to US population and medical practice
    - Competent clinical investigators
    - Data can be audited and validated by FDA

Global Opportunities

- Potential Advantages of Foreign Clinical Studies (advertisement by an Indian CRO)
  - Diverse population
    - Genetically
    - Culturally
    - Socio-economically
  - Large numbers of target patients
    - Quicker studies
  - Regulatory approval
  - Medical infrastructure
  - Language
  - Costs

Remember Murphy*!

- Poor infrastructure
  - Clinical complications
    - Simple problems could become significant, severe and….expensive
- Poor regulatory infrastructure
  - May limit acceptability of data
- Poor study control
  - May jeopardize collection of data
  - May disqualify patients
- Hence….
  - **Regulatory submission denial**

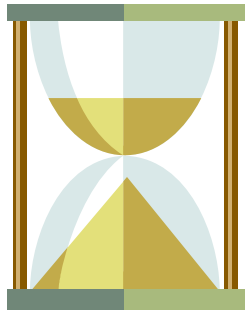
***Anything that can go wrong…will!**

Global Challenges – I

- Regulatory Approval
- Medical Infrastructure
  - Addressing adverse events
  - Access to healthcare system
  - Access to specialists
    - Addressing complications
  - Training investigators

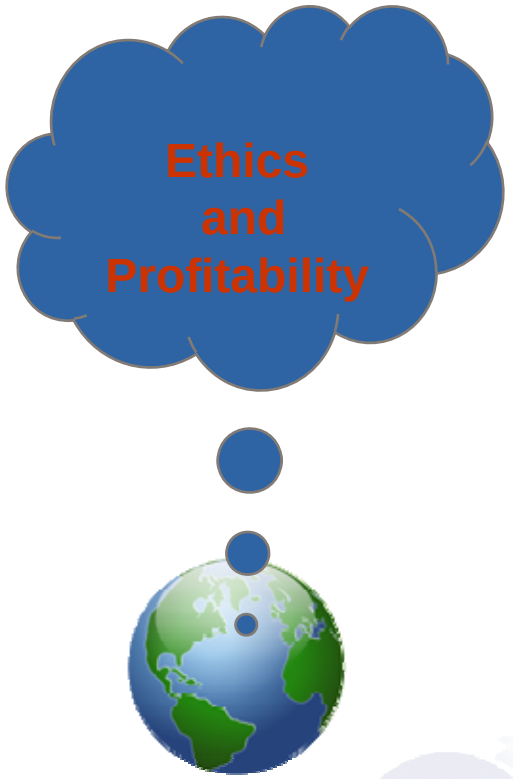
Global Challenges – II

- Language
  - Translation
    - Communication with patients, investigators
  - Validated questionnaires (e.g. QOL)
- Culture
  - Patient – clinician relationship
  - Collecting medical history (family, personal)
  - Medical tests
- Geography
  - Time
  - Distance
- Support

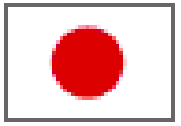


Global Limitations

- Review clinical plan with target regulators
  - In trial country
  - In target market
- Applicability of Clinical Data
  - Will target market accept trial data?
    - Regulators?
    - Clinical market?
- Validity of ‘Pooling’ Data
- Cost Information
  - Will it have any bearing on target market?
- Cost – Effectiveness Analysis
  - Is reimbursement an issue?



Global Trends



- Harmonization
  - Global Harmonization Task Force (GHTF)
    - Harmonize medical device regulations world-wide
    - Founding members (1992)
      - Regulatory authorities from Australia, Canada, EU, Japan and US
    - Five task forces, including one focused on clinical investigations
  - Global acceptance (and requirement) of GCP compliance
    - New FDA rule
- Opportunities
  - Site selectivity
    - It usually costs twice as much and takes three times longer (or vv)
    - If it is too good to be true….
- Challenges
  - Principal Investigator remuneration

Ethical Dilemmas (to ponder)

- Patient Enrollment
  - Monetary incentive
  - Clinician / patient trust (pressure?)
  - Full disclosure (risks, benefits, incentives)
- Study Conduct
  - Patient access to healthcare
  - Information dissemination to patients
  - Protocol requirements (tests, travel)
- Post-study
  - Availability of treatment

Thank You

Zvi Ladin, Ph.D.

Boston MedTech Advisors, Inc.

zladin@bmtadvisors.com
www.bmtadvisors.com

990 Washington Street
Dedham, MA 02026
Ph 781.407.0900
Fax 781.407.0901

Boston MedTech Advisors Europe, GmbH
Am Pastorenwaldchen 2
D-44229 Dortmund, Germany
Ph +49.231.973022.10
Fax +49.231.073022.31