Clinical trials in developing countries: Ethical issues

a- Basic principles
(b- Practical approaches)

Carel IJsselmuiden

COHRED
Council on Health Research for Development

ADVAC, Annecy, 19 May 2007

Ethics of Vaccine Trials – overview

1. Background & concepts
2. Short history of ‘health research ethics’
3. Some problems and tensions
4. Some solutions
5. Final reflection

Background and Concepts (1)

Ethical Theories

- ‘Deontological’ *(obligation-based)*
  - Religions, humanism, philosohpical
- Utilitarian *(consequence-based)*
- *Other: individualism, communitarianism, ethics of care*

Ethical Principles and Rules

- You shall not kill
- speaking the truth
- don’t do harm
- *and many more*

Ethical behaviour / Actions

- Informed consent before research
- conflict of interest statements
- plagiarism
- *etc*

And, in spite of greatly differing starting points, there is lots of agreement on ‘ethical’ actions

Background and Concepts (2)

- Principle based ethics
  - best known in research
  - ‘easiest’ to apply *(see further)*
  - but there are other approaches in ethics:
    - Value ethics, ethics of care, …

- **The 3 (4) ethical principles related to research:**
  - Principle of autonomy / ‘respect for persons’
  - Non-malfeasance (‘at least, do no harm’)
  - Beneficence (‘do good’)
  - Justice (‘distributive justice’ …)

Background and Concepts (2a)

From principle to practice:

1. autonomy / ‘respect for persons’
   - Informed consent process
2. Non-malfeasance (‘at least, do no harm’)
   - Animal evidence before human trials
   - technical competence of researchers
   - Taking care of trial induced complications
3. Beneficence (‘do good’)
   - Research in poor countries: provide capacity building
4. Justice (‘distributive justice’ …)
   - Fair distribution of risks and benefits

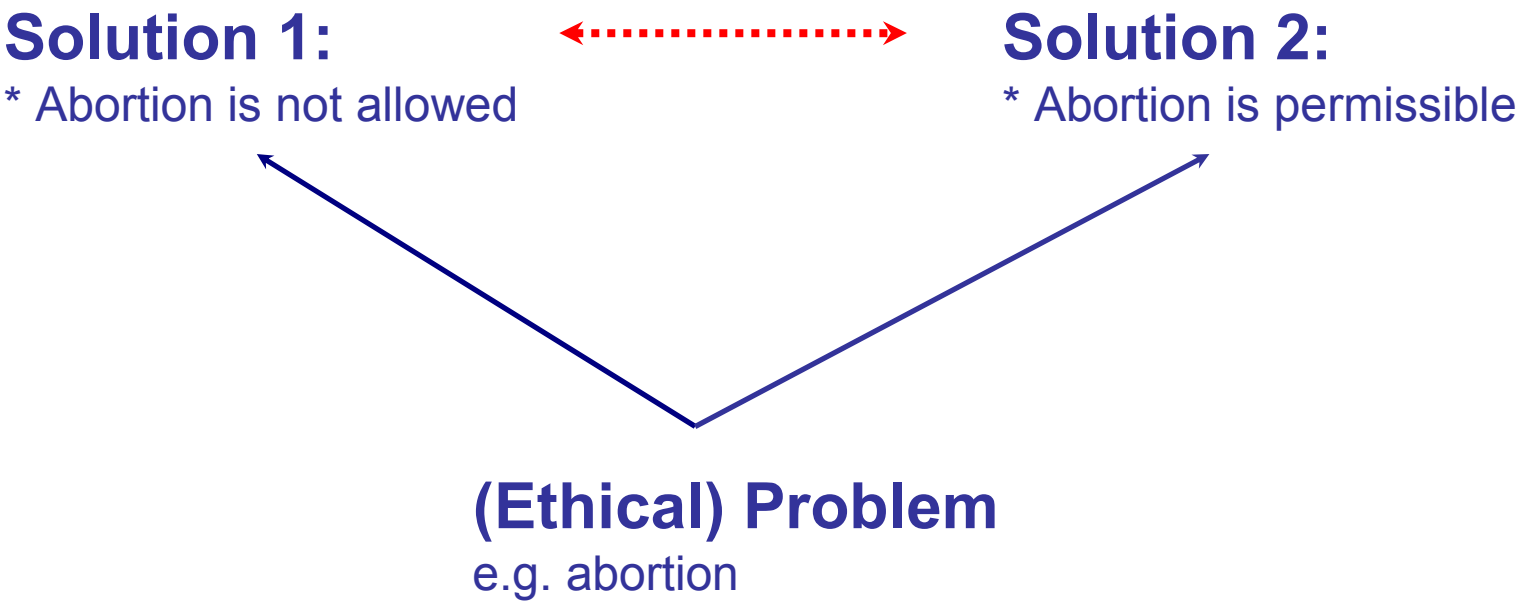
Can merge 2 and 3: ‘on balance: need to do more good than harm’

Background and Concepts (3)

- Principles: which is ‘most important ?’
  - not all are equal
    - *in ‘West’: autonomy is very dominant*
    - *may change over time*
    - *impact of lobby, activism, community involvement ...*
  - need to balance:
    - *don’t do this alone*
    - *ethics review committees*
    - *ethics expertise on trials (DSMBs)*

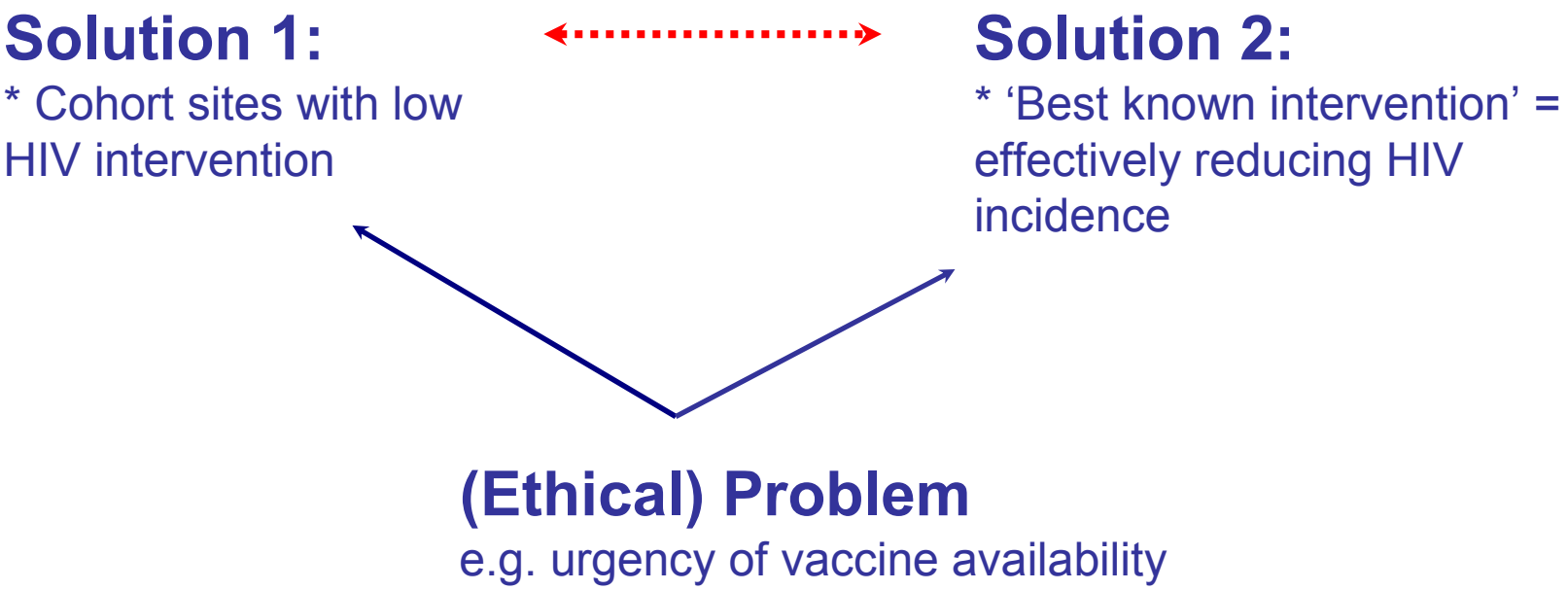
Background and Concepts (4)

- Ethical dilemma …



Background and Concepts (4a)

- Ethical dilemma …



Background and Concepts (5)

- ‘Equipoise’
  - to expose participants to a trial, researchers have to have a genuine uncertainty about the efficacy of the treatments being compared
  - but:
    - based on what evidence ?
    - can we ever really be uncertain ?
    - what about the use of placebo ?

Historical notes (1)

- Not much happened in bioethics until World War II
  - experiments on prisoners,
    - many fatal or disabling
    - all without freedom to refuse
  - Ended in war crimes tribunal in Nuremberg
    - **Nuremberg Code** (1948)
    - Not surprisingly: focused on autonomy of research participants, voluntariness of participation, and animal evidence before human trials
  - Still not much happened … as this was a military document

Historical notes (2)

- Nuremberg Code
- **Declaration of Helsinki** (1964):
  - World Medical Association
  - civil follow-up of Nuremberg
  - focused on many more issues
    - consent, highest possible care during research, welfare of patient is first priority, post research benefits, etc
  - Now in version 5 (2000) with amendments to paragraph 29 (2002) and 30 (2004)
  - Written for doctors … but used by all *(until now ?)*
  - Protection against abuse still major driver

Ethics Unit

Declaration of Helsinki

The Declaration of Helsinki is the WMA's best-known policy statement. It was first adopted in 1964 and has been amended five times since, most recently in 2000. Notes of clarification were added to para. 29 in 2002 and to para. 30 in 2004. The current (2004) version is the only official one; all previous versions have been replaced and should not be used or cited except for historical purposes.

- WMA Workgroup Report on the Review of Paragraph 30 of the Declaration of Helsinki (January 2004)
- WMA Secretariat Report on the Revision of Paragraph 30 of The Declaration Of Helsinki
- Documentation for the Preparation of Note of Clarification on Paragraph 30 of the Revised Declaration of Helsinki
- The International Response to Helsinki VI - The WMA's Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, as adopted by the 52nd WMA General Assembly, Edinburgh, October 2000
- "The World Medical Association's Declaration of Helsinki: Historical and Contemporary Perspectives" by Delon Human and Sev S. Fluss (Fifth draft 24/07/01)

See References

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World Medical Association
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Fax: +33 450 40 59 37
e-mail: wma@wma.net

Historical notes (3)

- Nuremberg Code
- Declaration of Helsinki (1964):

The New England
Journal of Medicine

Volume 274 JUNE 16, 1966 Number 24

Reprinted from pages 1354-1360.

SPECIAL ARTICLE

ETHICS AND CLINICAL RESEARCH*

HENRY K. BEECHER, M.D.†

BOSTON

HUMAN experimentation since World War II has created some difficult problems with the increasing employment of patients as experimental subjects when it must be apparent that they would

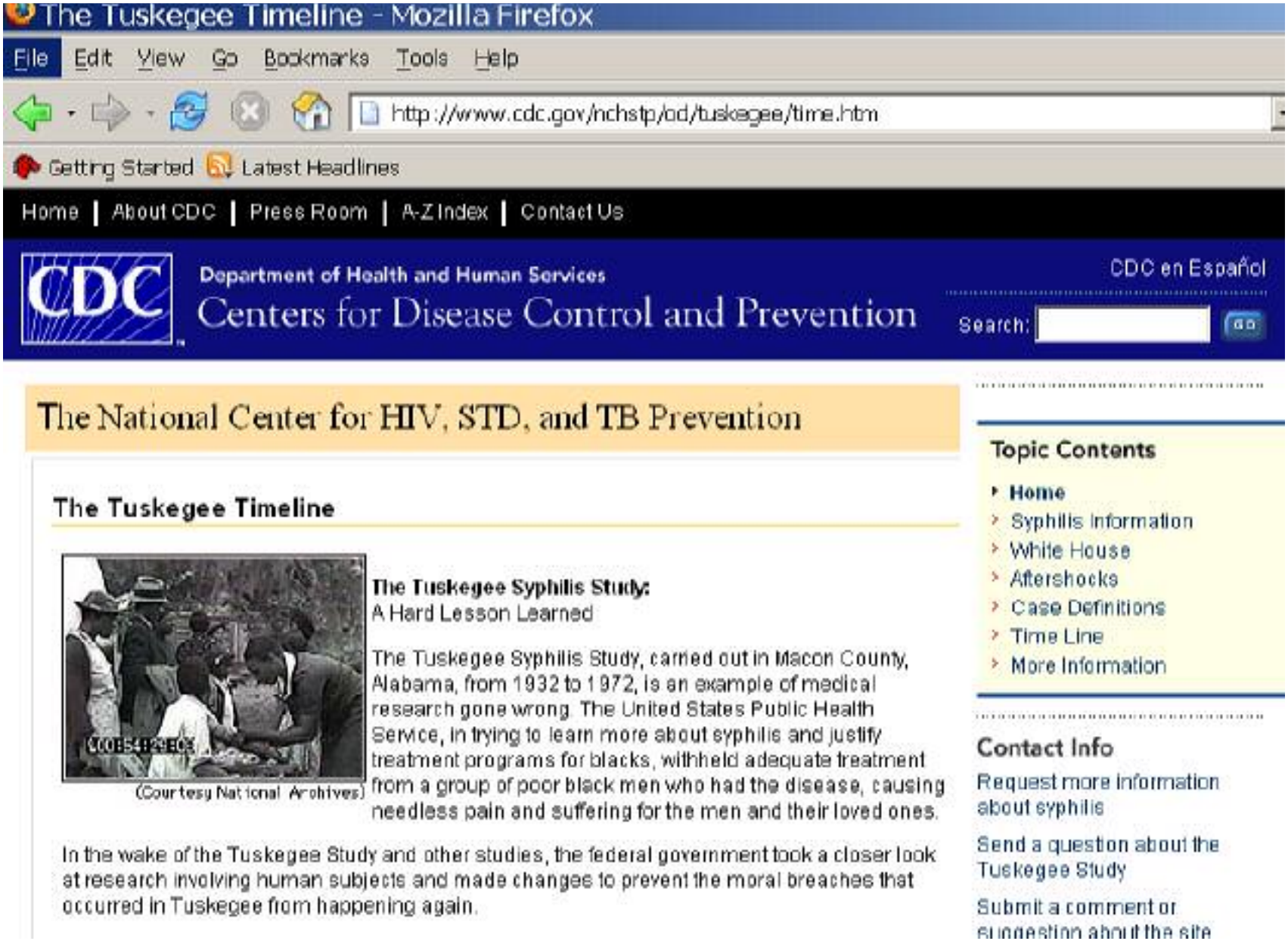
Experimentation in man takes place in several areas: in self-experimentation; in patient volunteers and normal subjects; in therapy; and in the different areas of *experimentation on a patient not for his bene-*

Council on Health Research for Development

Historical notes (3a)

- Nuremberg Code
- Declaration of Helsinki (1964):
- Beecher 1966

- **Examples (22) of unethical studies:**
  - Withholding of effective treatment:
    - Penicillin G against placebo for Rheumatic Fever in 109 men in the military
  - Improving understanding of disease:
    - injecting 'infectious hepatitis' in children in an institution of mentally defective children … to study the period of infectivity
    - Transplanting melanoma cells from daughter to mother
    - Injecting live cancer cells … to study immunity … without telling the patient; permission from hospital director
- Reinforced the need for ethics to protect participants against risks of research



In 1997, President Clinton apologized on behalf of the Nation

Historical notes (5)

- Nuremberg Code
- Declaration of Helsinki (1964):
- Beecher 1966
- Tuskegee
- In rapid succession (and all based on abuse prevention):
  - 1974 Belmont report
    - ('respect for persons' replaces 'principle of autonomy')
  - 1982 CIOMS
  - 1991 CIOMS Epi
  - and revisions …
  - 2005 UNESCO (Universal Declaration on Bioethics and Human Rights)

IRBs

AIDS activism: **benefits of research**

2006 : Global control: **clinical trial registration**

Problems and Tensions (1)

This paper was first presented and discussed at the Council's September 2002 meeting
It does not reflect the views of the Council or of the United States Government.

The Crisis in Human Participants Research: Identifying the Problems and Proposing Solutions

Anne Wood, M.A.
Christine Grady, Ph.D.
Ezekiel J. Emanuel, M.D., Ph.D.

Department of Clinical Bioethics
Warren G. Magnuson Clinical Center
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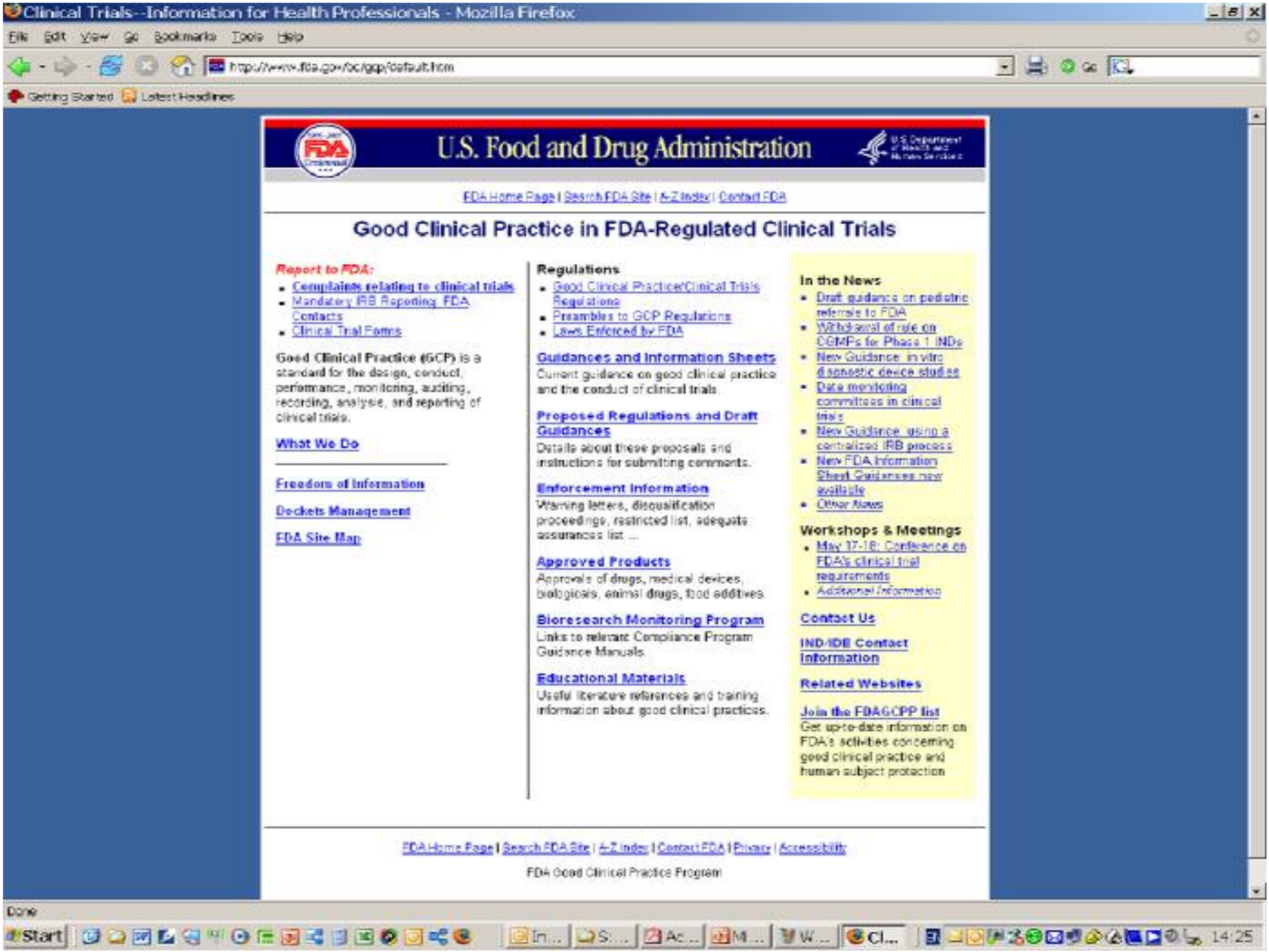
Clinical Trials--Information for Health Professionals - Mozilla Firefox
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Getting Started Latest Headlines
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Good Clinical Practice in FDA-Regulated Clinical Trials
Report to FDA:
Complaints relating to clinical trials
Mandatory IRB Reporting FDA Contacts
Clinical Trial Forms
Good Clinical Practice (GCP) is a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials.
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Dockets Management
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Regulations
Good Clinical Practice/Clinical Trials Regulations
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Laws Enforced by FDA
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In the News
Draft guidance on pediatric referrals to FDA
Withdrawal of rule on CGMPs for Phase 1 INDs
New Guidance: in vitro diagnostic device studies
Data monitoring committees in clinical trials
New Guidance: using a centralized IRB process
New FDA Information Sheet Guidances now available
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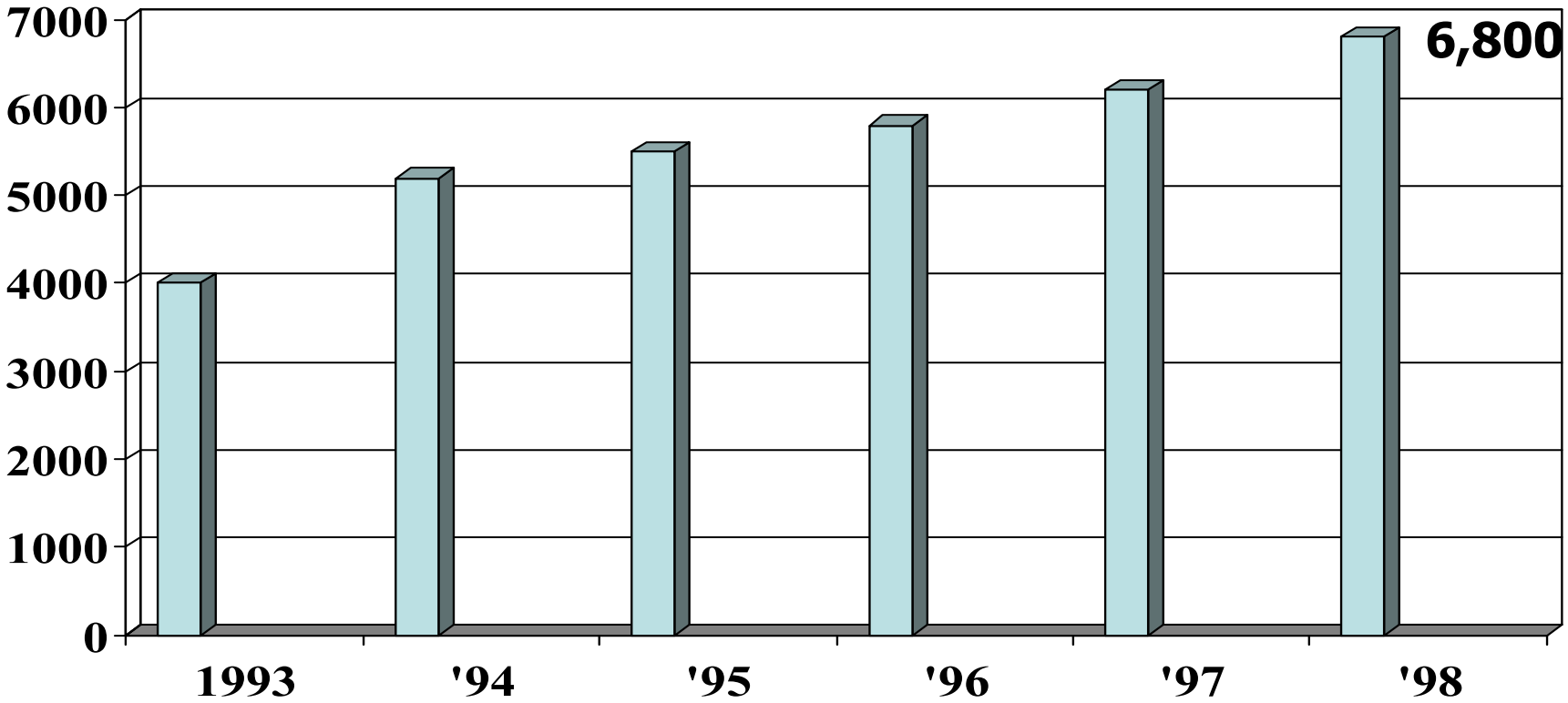
FDA Good Clinical Practice Program
Done
Start
14:25

Problems and Tensions (3)

- Trials increase massively in number
  - more drugs … more trials
  - more regulatory demand for trial evidence
  - therapeutic margins of improvement lower – bigger samples, more time, less chance of success …
    - multi-centre trials
    - debate about ‘ethics vs science’

Slide from Melody Lin, DHHS, USA, 2002

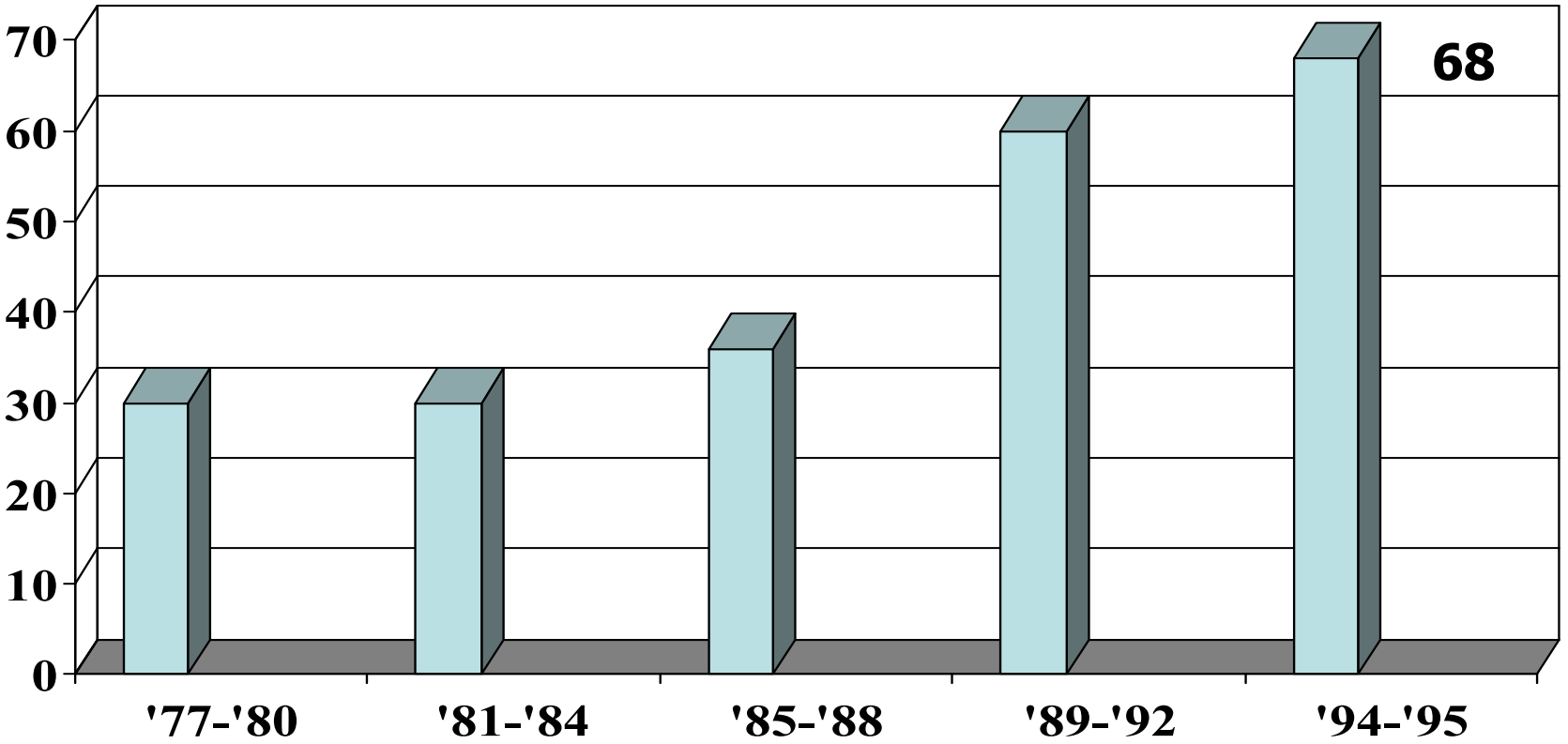
Estimated Number of Drugs Being Developed Worldwide



Sources: FDA Biomonitoring Research database; Parexel's Pharmaceutical R&D Statistical Sourcebook 1999; Aculaunch; Washington Post Research

Slide from Melody Lin, DHHS, USA, 2002

Average Number of Clinical Trials per New Drug Application



Sources: FDA Biomonitoring Research database; Parexel's Pharmaceutical R&D Statistical Sourcebook 1999; Aculaunch; Washington Post Research

Problems and Tensions (3)

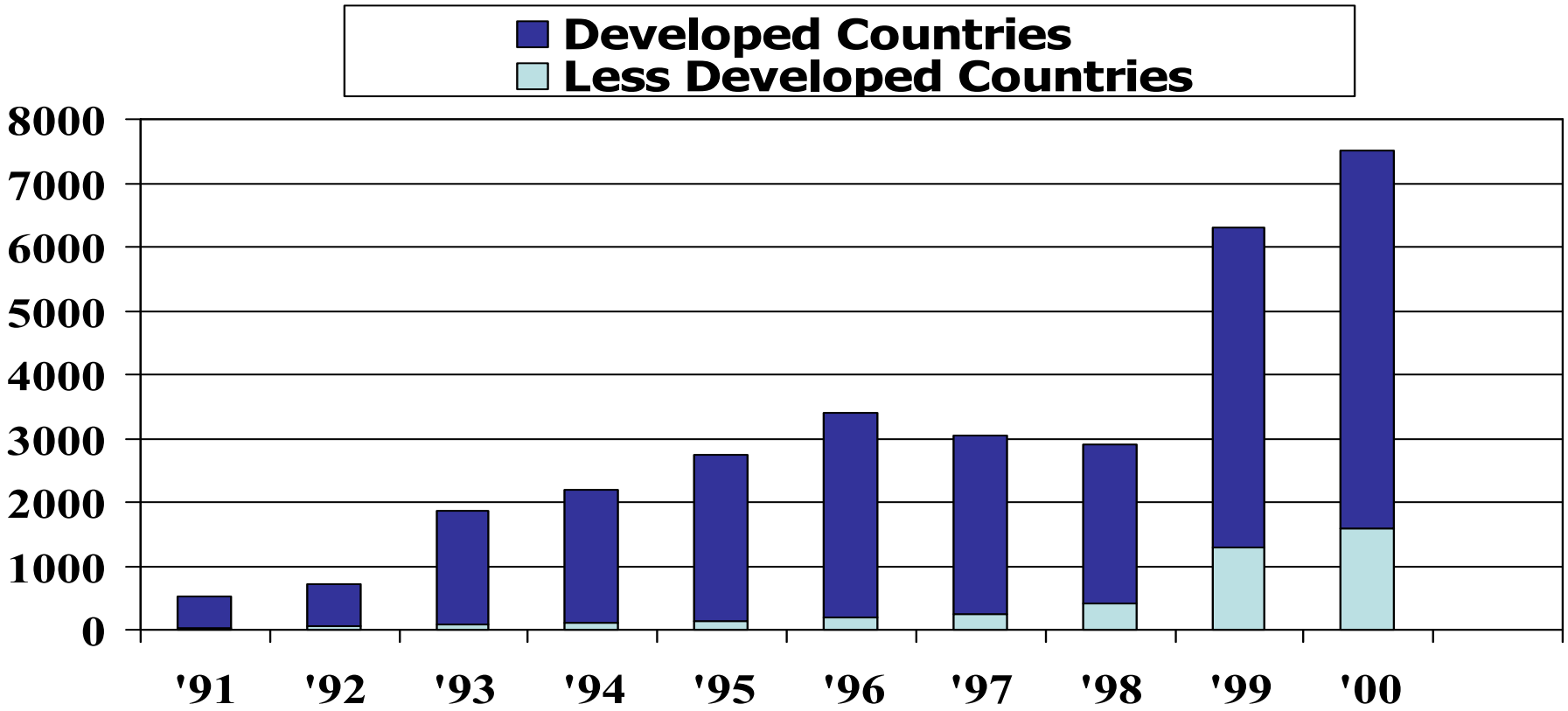
- Trials increase massively in number
- The increase is also – even especially – in developing countries

  – e.g. EDCTP


EDCTP
European and Developing Countries Clinical Trials Partnership
Contact us | Site
EDCTP Vision
By 2012, European research within the 3 poverty related diseases may operate as joint programmes with pooling of resources and thus maximizing the benefit of their research.

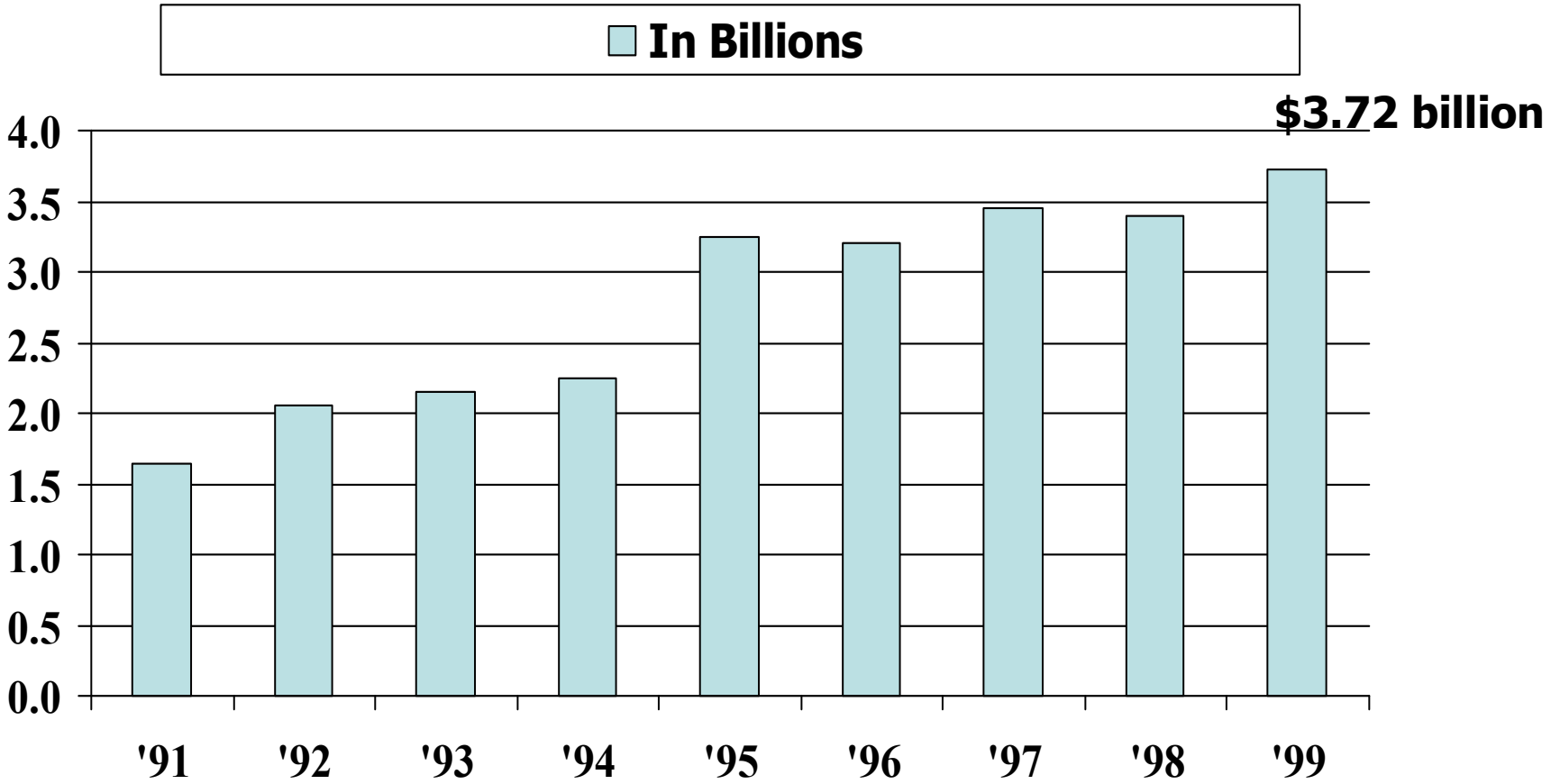
Slide from Melody Lin, DHHS, USA, 2002

Number of Overseas Human Clinical Trials for New Drugs



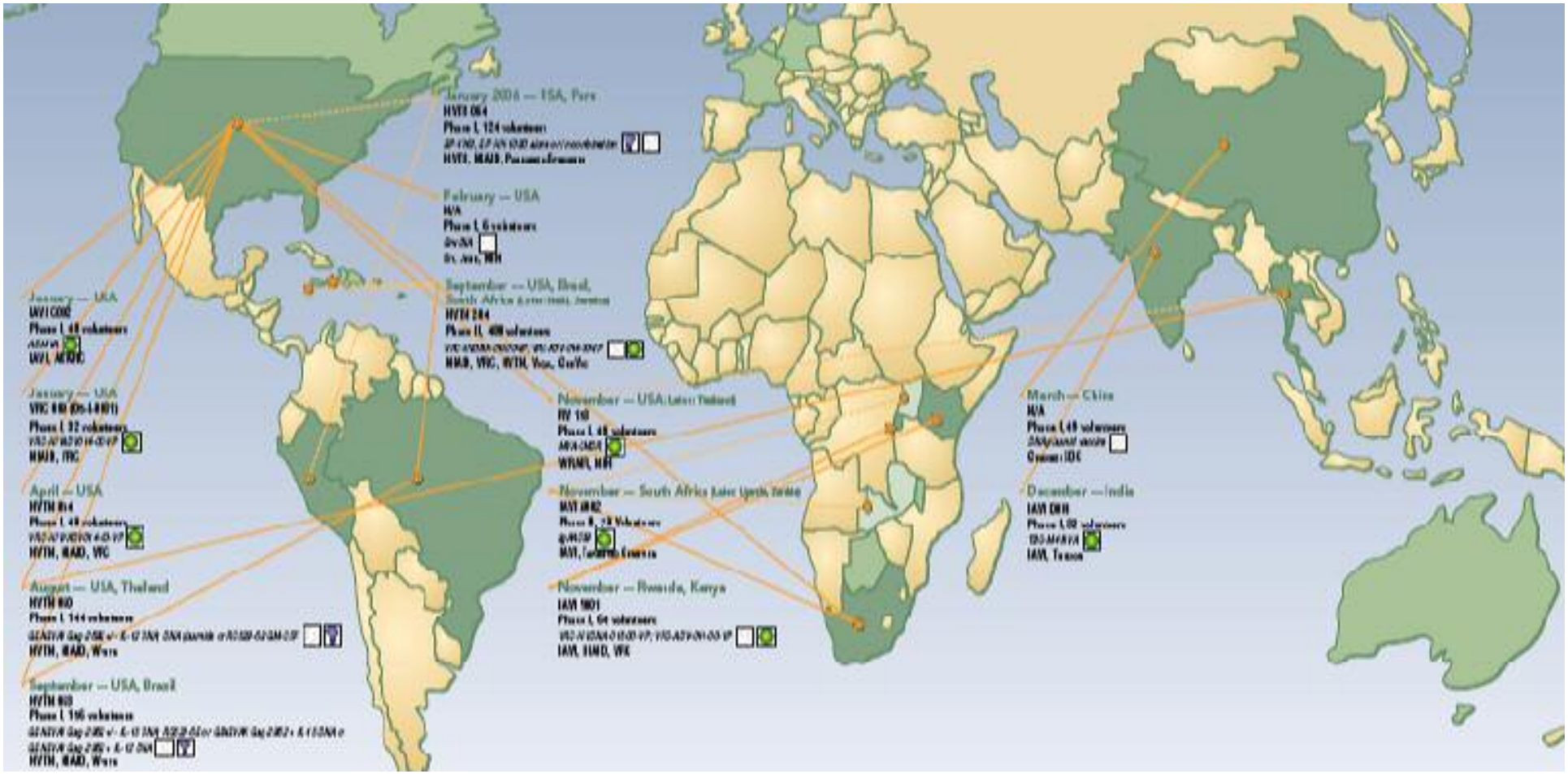
Sources: FDA Biomonitoring Research database; Parexel's Pharmaceutical R&D Statistical Sourcebook 1999; Aculaunch; Washington Post Research

Overseas Spending by U.S. Pharmaceutical Companies

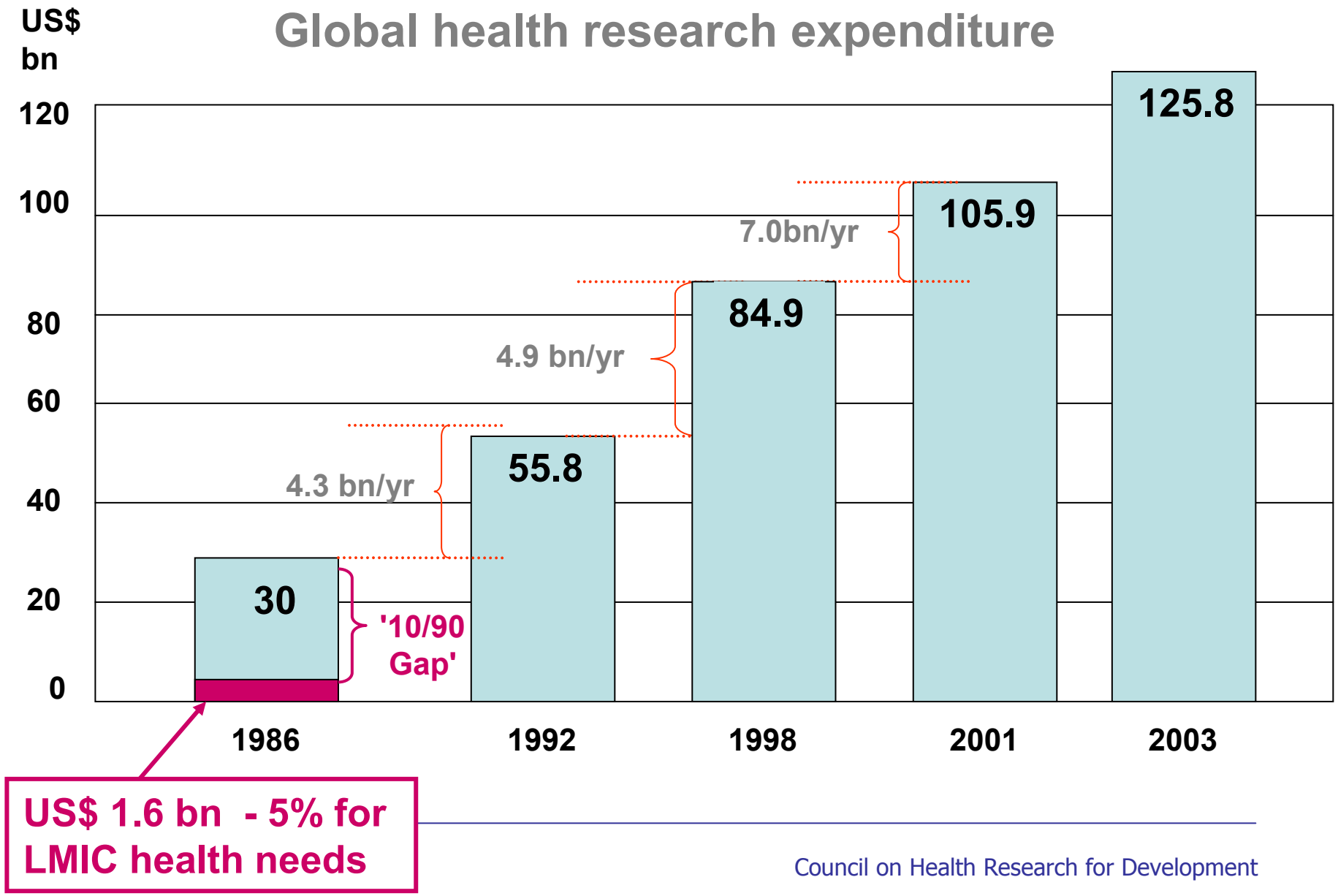


Sources: FDA Biomonitoring Research database; Parexel's Pharmaceutical R&D Statistical Sourcebook 1999; Aculaunch; Washington Post Research

AIDS Vaccine Trials and Sites



Source: Adapted from Global Forum for Health Research, Geneva 2006

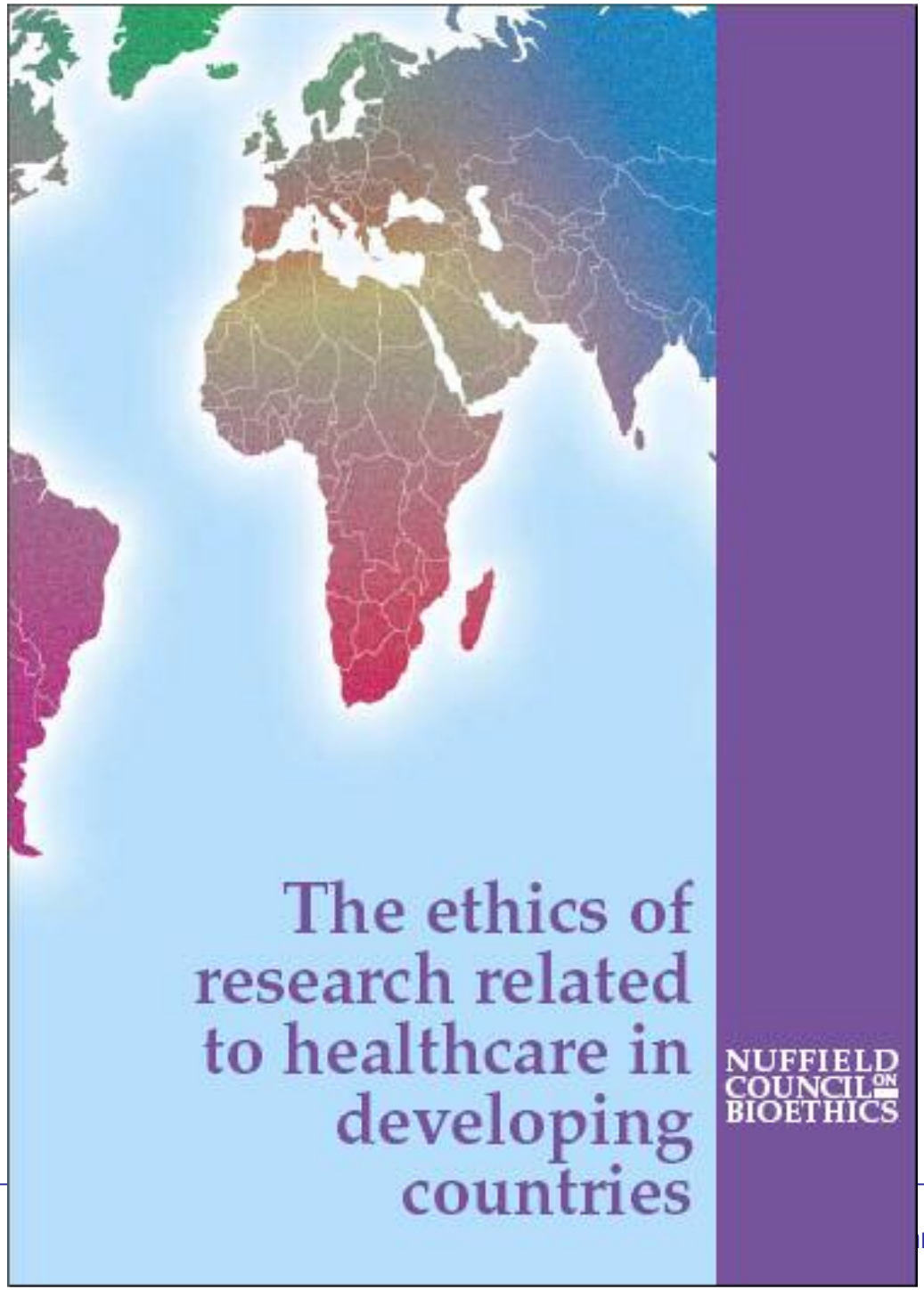


Problems and Tensions (4)

- Health research in developing countries puts major ethical challenges:
  - Very low ethics review capacity : so who reviews and decides ?
  - Issues of data ownership
  - Issues of technology transfer
  - Issues of (un) equal research partnerships
  - Intellectual Property Rights – no way to enforce

Problems and Tensions (4a)

- Health research in developing countries puts major ethical challenges:
  - Low income:
    - No ‘referral’ system to send patients to
    - No ability to purchase care
  - Lack of legal infrastructure:
    - No ability to obtain legal recourse
  - Lack of understanding of the research enterprise:
    - Difficulties in obtaining informed consent
  - Lack of democratic culture:
    - Nature of ‘voluntariness’ *(generally or gender-specific)*

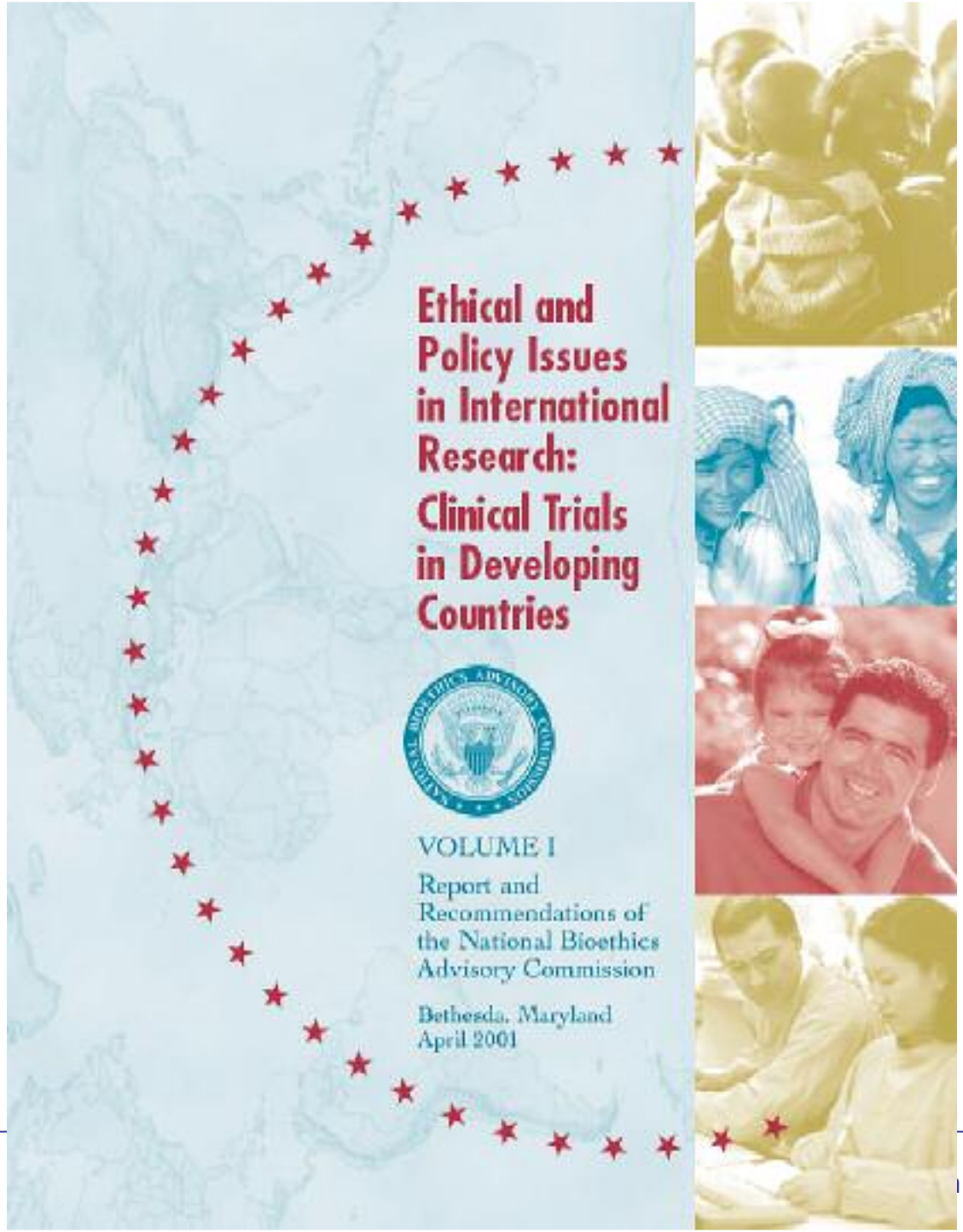

The ethics of research related to healthcare in developing countries
NUFFIELD COUNCIL ON BIOETHICS

Ethical considerations in HIV preventive vaccine research

UNAIDS guidance document

UNAIDS 2000

ırch for Development


Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries
VOLUME I
Report and Recommendations of the National Bioethics Advisory Commission
Bethesda, Maryland
April 2001

Some solutions (1)

- **Build capacity for ethics review**:
  - NIH is lead agent : since 1999
  - Wellcome Trust, MRC UK, other follow … but less intensive
  - EU is only very recently joining
  - Global Forum on Bioethics in Research (GFBR)
    - Forum 8: Vilnius, Lithuania, 27-29 June 2007: fostering the research ethics infrastructure in the developing world / transition societies; and ethical aspects of mental health research

Global Forum On Bioethics in Research - Mozilla Firefox

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What is the Forum?

The Global Forum on Bioethics in Research is an informal partnership established by a number of organizations with a shared interest in the ethics of conducting research involving human beings in developing countries. The Forum meets approximately annually, with an emphasis on discussion. The first meeting was in Bethesda in 1999, the second in Bangkok in 2000, the third in Cape Town in February 2002, and the fourth in Brasilia in October 2002. The fifth will be in Paris in 2004. Each annual forum has a main organiser: National Institutes of Health for 1999, World Health Organisation for 2000, Medical Research Council (UK) for Cape Town 2002, Pan American Health Organisation for Brasilia 2002, and INSERM for 2004.

What are the aims of the Forum?

Latest News

NEW!

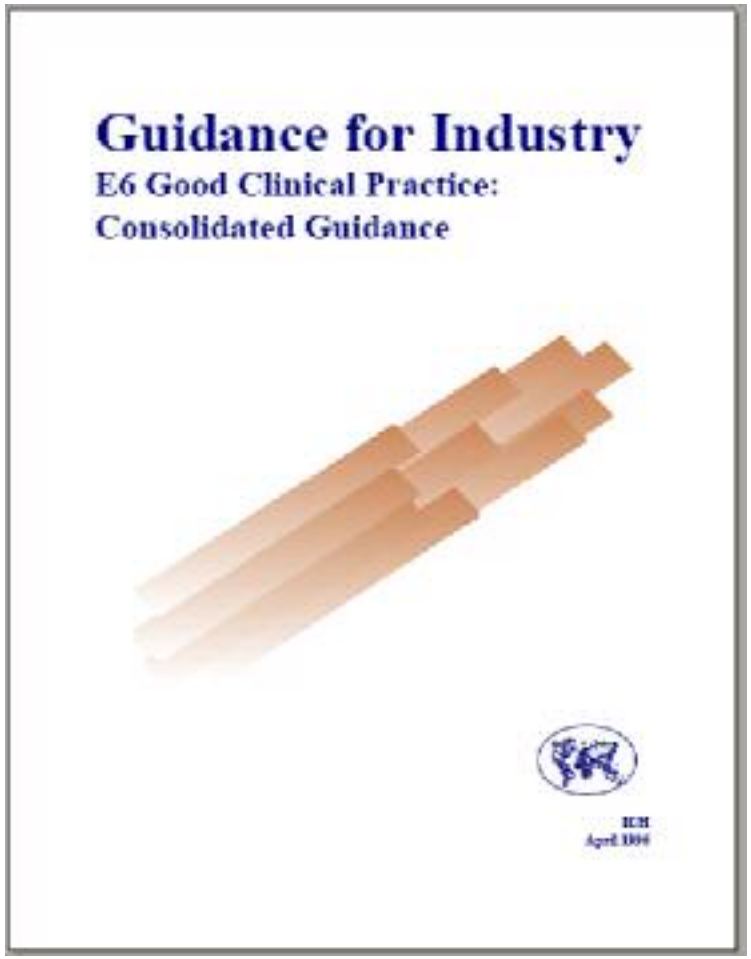
Global Forum on Bioethics in Research

Call for Proposals to Host Forum 8 (in 2007) and Forum 9 (in 2008)

The Steering Committee of the Global Forum on Bioethics in Research invites applications from interested

Some solutions (2)

- **International Conference on Harmonisation**
  - Attempt to reduce need for multiple review of same protocols across countries
  - Driven by industry, and by industrial nations (EU, Japan, USA)
  - Good principle, but …
    - Asks countries to give up autonomous decision making just at ethics review capacity is being built
    - And, does not address IP / technology transfer *



HANDBOOK FOR GOOD CLINICAL RESEARCH PRACTICE (GCP)

GUIDANCE FOR IMPLEMENTATION

World Health Organization

WHO, 2002

Some solutions (3)

- **Revise the Helsinki declaration** (and others)
  - *or … ignore it*
- **Paragraph 29:** trials need to test against best currently known treatment
  - What about vaccine trials ?
- **Paragraph 30:** post-trial access to 'best proven' treatment
  - But whose responsibility ?
  - And … only to participant, or wider ?

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. See footnote

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study. See footnote

Note: Note of clarification on paragraph 29 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

Page back to paragraph 29.

Note: Note of clarification on paragraph 30 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

Some solutions (4)

- New attempt … to bring ‘reason’ into the conduct of trials:

- WHO consultation on ‘governance’ of research, in addition to science and ethics
  - Already in use in MRC UK
  - Bring in ‘best research governance’ in addition to ethical ‘yes’ or ‘no’ or ‘morally praiseworthy’
    - Problem is: who will take the extra effort ?

Degree of responsibilities for care and treatment provision in the context of vaccine trials

WHO Tarantola 2006

Eligibility for care and treatment	Obligation by current ethical review process	Best Research Governance	"Morally Praiseworthy"
Trial participants: care and treatment for target disease	Obligation set by existing guidelines	Obligation accepted by all stakeholders	Obligation recognized
Trial participants: care and treatment for linked diseases	No obligation stipulated	Must be considered	May be considered
Trial participants: care and treatment of other severe diseases	No obligation stipulated	Must be considered	May be considered
Non-trial participants: care and treatment for target disease	No obligation stipulated	Must be considered	May be considered
Non-trial participants: care and treatment for other severe adverse events	No obligation stipulated	Must be considered	May be considered

Final Reflections (1)

Ethics … to protect participants against abuse

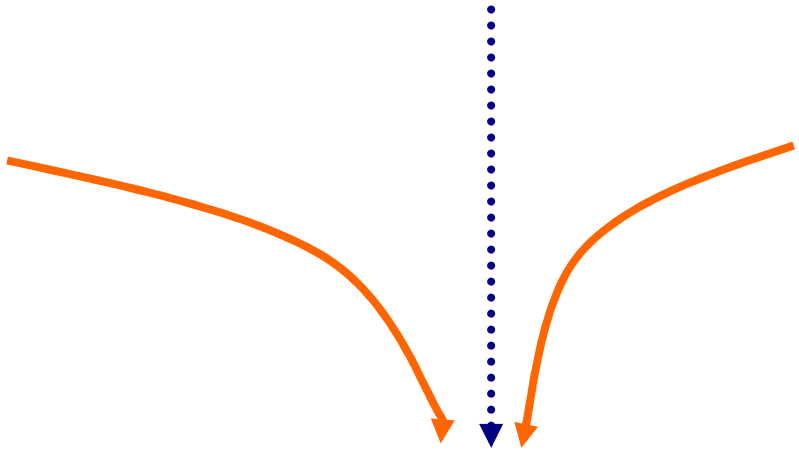
Ethics … to provide participants with fair benefits

Activism & Human rights

* ‘soft’
* ‘hard’

Negotiation

Research as part of development



Actual practice

AIDS Vaccine Clearinghouse

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- Policy
- Global Access
- Comprehensive Response to AIDS
- Global HIV Vaccine Enterprise
- Advocates' Network
- PrEP Watch

Welcome to the AIDS Vaccine Clearinghouse, a gateway to information and a link to other people and organizations concerned about AIDS vaccine advocacy, research, and global delivery. The Clearinghouse welcomes submissions of documents, translations, announcements and events.

Submissions to the Clearinghouse
If you wish to submit a document or event to the Clearinghouse, please contact us at: clearinghouse@avac.org.

Developed, Edited and Sponsored By:

AVAC
AIDS Vaccine Advocacy Coalition

What's New

AVAC launches AIDS Vaccine Clearinghouse, a comprehensive and interactive source of AIDS vaccine information on the Internet. *Click here for the announcement.*

May 18th, HIV Vaccine Awareness Day, is designed as a day to educate communities about the importance of HIV vaccine research and thank the thousands of volunteers who have participated in clinical trials. *Click here for a list of events around the world.*

Join AVAC's *Advocates' Network,* an electronic resource for organizations and individuals interested or already involved in advocacy for the development of vaccines for HIV/AIDS. The Advocates'

Towards the case study

- Use CIOMS & Helsinki to phrase answers
  - or others, if you want
- Try to steer away from ‘personal experience’
- *But, ethics of research is (still) developing, so there will be areas where there are no guidelines … the true place to explore the application of ethical principles and rules !*

Council for International Organizations of Medical Sciences
(CIOMS)

CIOMS

International Ethical Guidelines for Biomedical Research Involving Human Subjects

The Council for International Organizations of Medical Sciences (CIOMS) announces the publication of its revised/updated *International Ethical Guidelines for Biomedical Research Involving Human Subjects*.

This 2002 text supersedes the 1993 Guidelines. It is the third in the series of biomedical-research ethical guidelines issued by CIOMS since 1982. Its core consists of 21 guidelines with

The Guidelines relate mainly to *ethical justification and scientific validity of research; ethical review; informed consent; vulnerability of individuals, groups, communities and populations; women as research subjects; equity regarding burdens and benefits; choice of control in clinical trials; confidentiality; compensation for injury; strengthening of national or local capacity for ethical review; and obligations of sponsors to provide health-care services.*

Their scope reflects the changes, the advances and the controversies that have characterized biomedical research ethics in the last two decades. Like those of 1982 and 1993, the 2002 CIOMS Guidelines are designed to be of use to countries in defining national policies on the ethics of biomedical research involving human subjects, applying ethical standards in local circumstances, and establishing or improving ethical review mechanisms. A particular aim is to reflect the conditions and the needs of low-resource countries, and the implications for multinational or transnational research in which they may be partners.

ISBN 92 9036 075 5

Price: Swiss francs 20.

Order from CIOMS,
c/o WHO, Avenue Appia 20,
CH1211 Geneva 27, Switzerland.

Ethical issues in HIV vaccine trials in South Africa

C. Slack[a*], G. Lindegger[a], E. Vardas[b], L. Richter[a], A. Strode and D. Wassenaar[a]

IN THIS REVIEW WE DESCRIBE THE ETHICAL issues central to local and international debates about HIV vaccine trials. These issues include the physiological and psycho-social risks of trial participation, the preventative interventions to be provided to participants, access to treatment for participants who seroconvert, access to an effective vaccine after the trial, the role of placebo-controlled trials, and obtaining informed consent.

control for the possible impact of such factors on trial outcomes.

Vaccine trials may be alien or unwelcome concepts in communities from which participants for trials are drawn. A counter-view posits that, since other forms of immunization and vaccination are already so widespread, HIV vaccine trials may be perceived as extensions of familiar health protective practices. Community

the theoretical basis, design or analysis is fundamentally flawed, are likely to be considered unethical. Such studies waste resources and may foster false expectations that have no possibility of being met, so, from this perspective, good science is a necessary component of sound ethics.[1a]

Comparatively little is written about the reciprocal way in which sound ethics are a necessary component of good science. The ethical principles of autonomy, beneficence and justice are inscribed in research practices such as informed consent and the protection of confidentiality. These inscriptions tend to be approached as 'add-ons' to scientific procedures rather than intrinsic to them; as additional requirements necessitated by increased sensitivity to human rights in scientific and other spheres of life.

Evidence exists, however, that procedures in scientific investigations associ-