

Comtemporary ethical
controversies
in clinical research

- ❖ *Clinical research in developing countries*
- ❖ *The use of placebos*
- ❖ *Protection for communities*

The World Medical Association (WMA)

(Sept. 19, 2000)

« Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research. The protocol presented to the ethical review committee must include a realistic plan to deliver those treatments identified through such research to the populations from which the subjects have been drawn »

What makes clinical research ethical

(E.J. Emanuel et al JAMA May 2000)

1. *Social or scientific value of treatment or intervention that will improve health, well-being or knowledge*
2. *Respect for subject autonomy and welfare*
 - . *Permitting withdrawal*
 - . *Informing of newly discovered risks or benefits*
 - . *Informing of results of clinical research*
3. *Informed consent :*
 - . *Purpose of the research*
 - . *Potential risk, benefits*
 - . *alternatives*
4. *Favorable risk-benefit ratio ; nonmaleficence, beneficence and non exploitation*
5. *Fair subject selection ; not targeted to stigmatized and vulnerable individuals or population*

6. *Independant review ; minimizing potential conflicts of interest*
7. *Scientific validity ; to produce reliable and valid data*

There is a need to strengthen
protections for humans
subjects

Because of :

- ❖ *Aggressive recruiting and erosion of informed consent due to pressure from industry to recruit subjects quickly*
- ❖ *No adherence to standards of good clinical practice :*
 - . *Failure to disqualify subjects who did not meet the criteria for a study*
 - . *Failure to report adverse events*
 - . *Failure of adequate training of research staff*

❖ *Excessive workloads and inadequate resources of institutional review boards.*

❖ *Ethical dilemmas :
« Is Academic Medicine for sale ? »
(Marcia Angell)*

The paradigm of pregnant women infected with HIV

The first placebo controlled trial in 1994 :

Protocol 076, USA

❖ *HIV testing and counseling to all women*

❖ *Lengthy oral regimens with AZT/vs placebo*

❖ *Intravenous administration of AZT at delivery*

- ❖ *Refrain from breast -feeding*
- ❖ *6 w. AZT for the new born estimated cost ± 800\$ per mother and infant*
- ❖ *AZT is superior to placebo*
- ❖ *Vertical transmission decrease from 30% to 7%*

From « Good Clinical Practice »
to Ethical « Relativism »

Pregnant women with HIV
infection :

1997 : « *Even though 076 protocol is effective in some countries, it is unlikely that it can be successfully exported to many others* » (Harold Varmus, Nobel Prize, Director NIH)

Ü Studies of alternative regimens in some countries :

« The most compelling reason to use a placebo controlled arm is that no current intervention is standard practice and placebo-controlled study provides a faster response

and definitive answers to questions about safety and value of an intervention in the setting in which the study is performed"

Ethical relativism

The case of HIV infected pregnant women :

1999 Nevirapine study in Uganda

- . 13.839 women HIV tested*
- . 2.144 (15.49%) seropositive*
- . 645 randomised after « written informed consent »*

AZT 2 doses (600mg)

versus NVP 1 dose (200 mg) at delivery

Results : NVP is superior to Zidovudine

In fact :

- ❖ *Controlled arm is equivalent to a placebo*
- ❖ *AZT was used at infratherapeutical doses*
- ❖ *No follow up and no treatment of the mothers after delivery : VL : 28.000 !*
- ❖ *No treatment of the children even if they are tested (VL, immunity, culture HIV) until 18 months !*

The Ethical « Relativism »

❖ *Double standards for research in developed versus developing countries.*

Ü

- ❖ *The standard of care in the control group could be less effective therapy or no therapy*
- ❖ *The treatment is abandoned when the trial ends*
- ❖ *The interest of « Science » prevails over the interest of the patients*

« As long as drug companies need to show their drug is better than existing therapies, they will think they have to use the worst recommended therapy as a comparison.

It really requires some fundamental rethinking of the FDA »

Robert Yarchoan, N.C.I., April 1997

Limitations of industry sponsored anti HIV trials

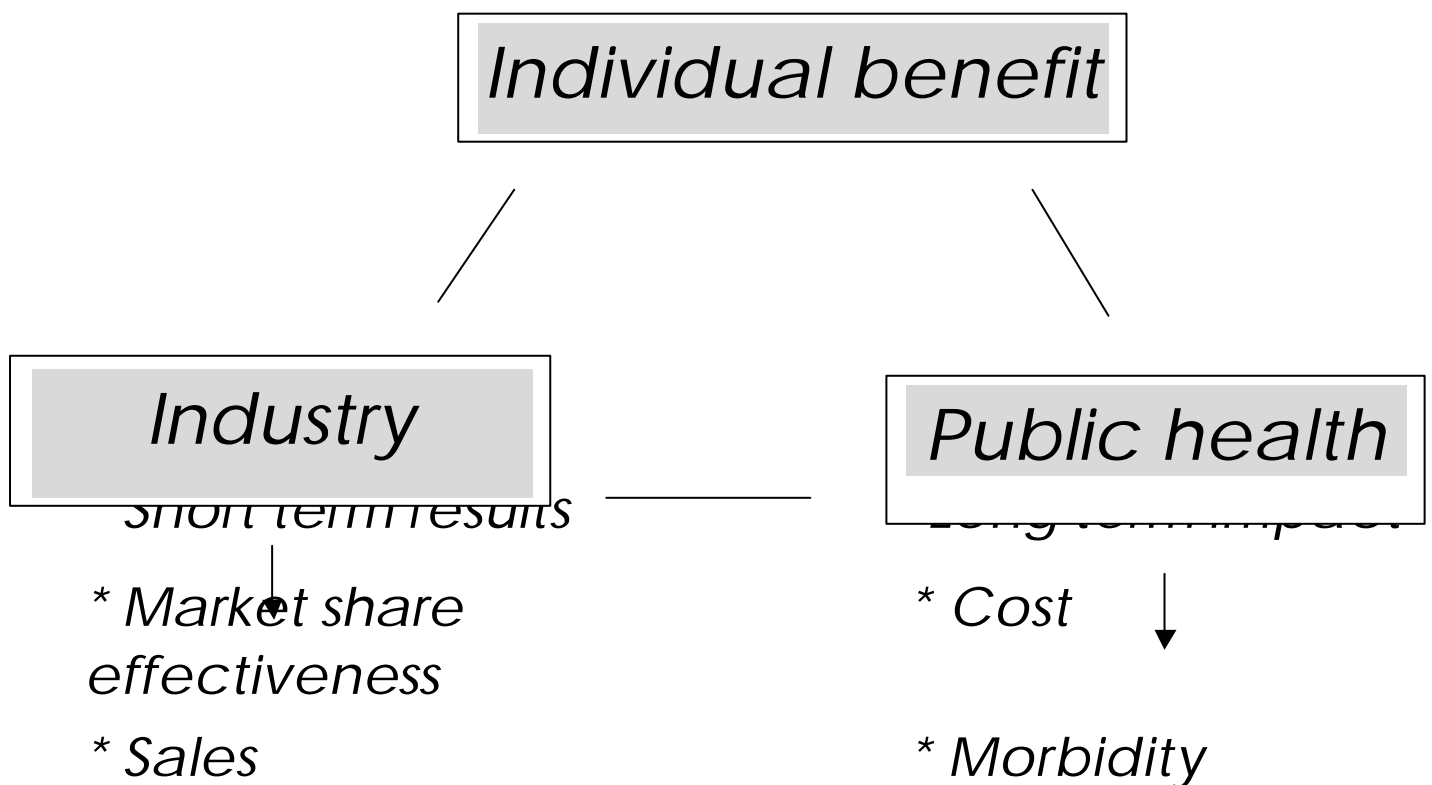
- ❖ Short or Medium term objectives
 Y lack of long term follow up
 (post marketing studies)
- ❖ *Need to comply with regulatory requirements Y rigidity*
- ❖ *Lack of physiopathological perspective*
- ❖ *Drug oriented trials and risk of « single company » oriented trials (« incestuous » trials)*

THE CLINICAL RESEARCH :
IN WHOSE BEST INTEREST ?

UNIVERSALIAN
OR
UTILITARIAN
ETHIC ?

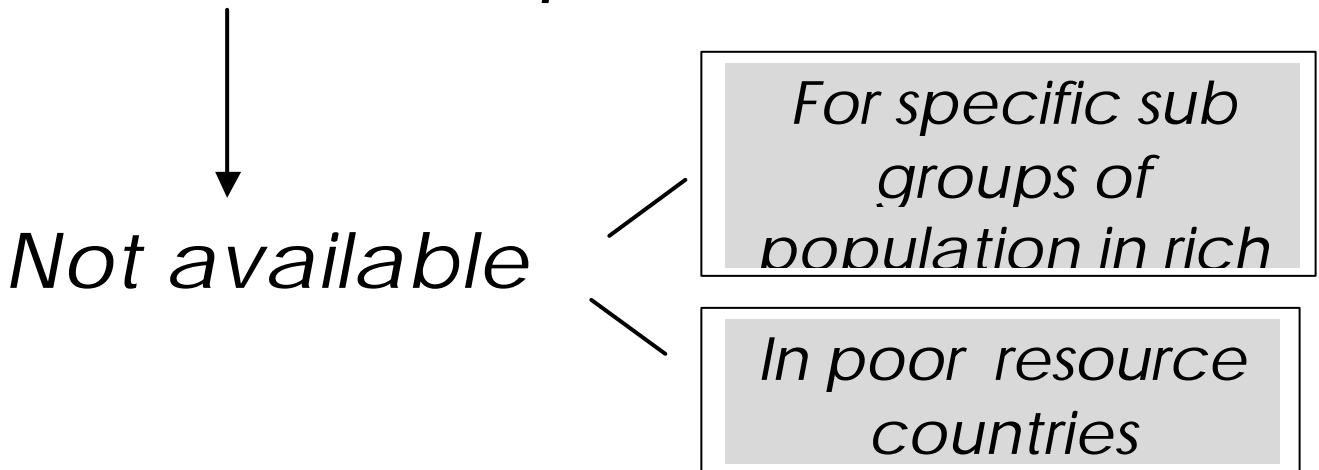
Potential conflictual issues in anti HIV clinical trials

Strategies for Optimal care



Constraints of current anti HIV treatments

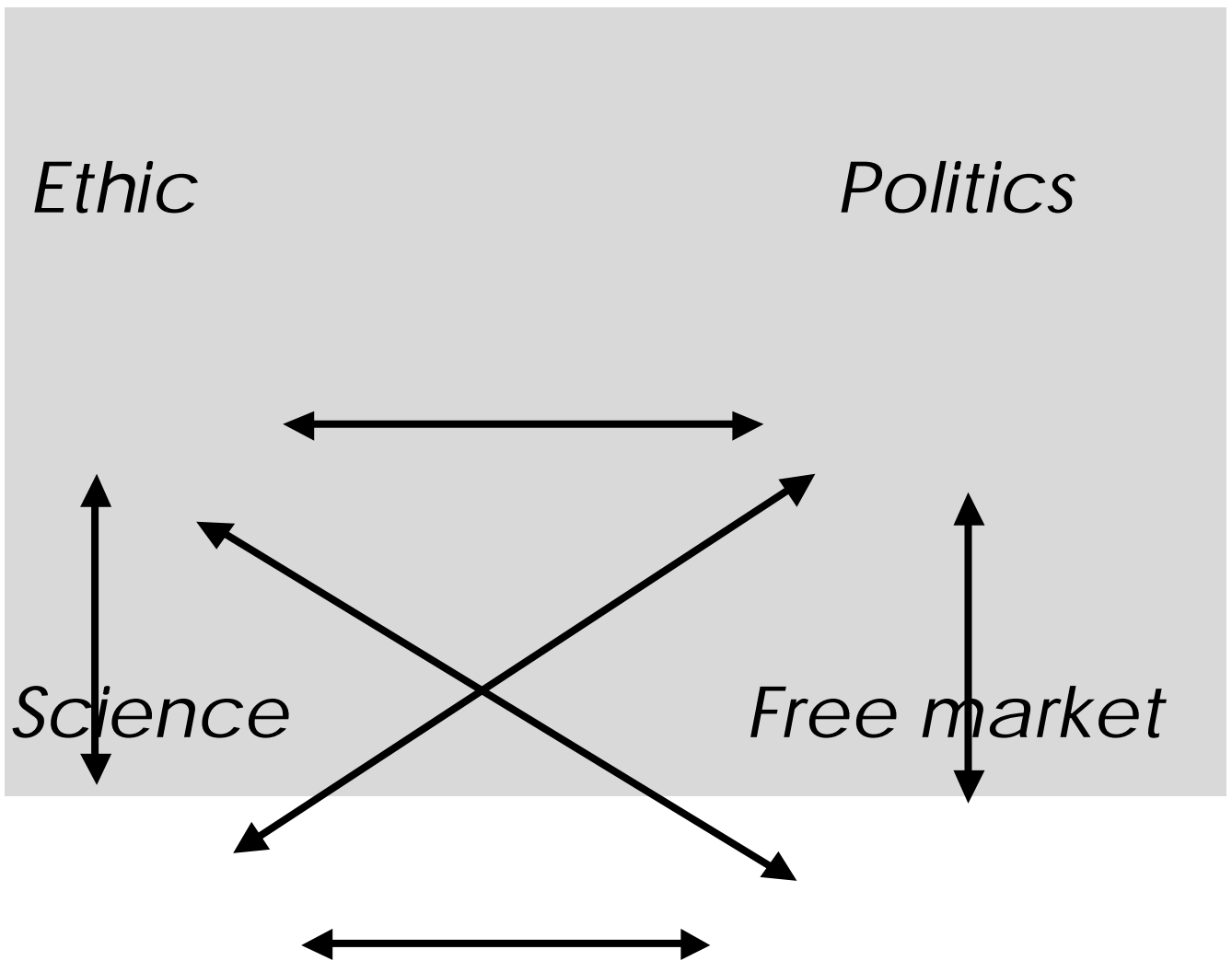
- ❖ *Diagnostic testing*
- ❖ *Drugs available*
- ❖ *Compliance*
- ❖ *Monitoring of therapy*
(Resistance, blood levels, side effects)
- ❖ *Access to specialized care units*



Issues related to these ethical controversies

- ❖ *The value of « informed consent »*
- ❖ *The ethics of subject selection*
- ❖ *Appropriate risk-benefit ratios*
- ❖ *The value of research to society*
- ❖ *The provision of treatment to research participants.*

HIV epidemic :
a new paradigm



Déclaration d'Helsinki

“ In research on man, the interest of science and society should never take precedence over considerations related to the well being of the subjects ”.

“ In any medical study, every patient, including those of a control group, should be assured of the best proven diagnostic and therapeutic method ”.

The Lancet Editorial

(Sept. 30, 2000)

« This is a deep disappointment to those who feel that these principles are illogical and impractical »