ETHICAL AND SCIENTIFIC STANDARDS IN RESEARCH

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INTRODUCTION

Approximately one year ago, the Foundation Víctor Grífols i Lucas called together a series of experts in order to discuss the subject of this monograph *Ethical and Scientific Standards In Research.* For a foundation devoted to considering bioethics, the objective naturally focuses on biomedical research, particularly clinical trials with medicinal products. Since the idea consists of analyzing the standards or criteria that would make exposure to certain risks legitimate, we began by comparing and contrasting the developed world and the developing world, assuming perhaps that the scientific and ethical standards for the two may allow for some variation.

The discussion was based on two presentations discussing the two aforementioned perspectives by Prof. Silvio Garattini (Italy) and Prof. Solomon Benatar (South African Republic) as spokespersons for the developed world and the developing world, respectively. The clarity and diversity of the aspects presented by both of them resulted in considerable discussion that is transcribed after the text of each speaker.

Although I run the risk of not doing justice to the variety of issues raised during the debate, I feel I should mention that there were two main topics that polarized the opinions expressed by those taking part. The first is more directly related to the question initially proposed and involves relativization, or rather the inevitable "contextualization" of some scientific and ethical standards that, regardless of how universal they are intended to be, must be adapted to each particular case. Social and economic diversity cannot be dealt with unless we show some flexibility. In fact, an excessively "paternalistic" viewpoint could lead to simply preventing risks, thereby slowing down both the progress of knowledge and specific benefits for certain human groups. Simply because it is neither legitimate nor ethical to merely say there must be differing measuring standards (depending on the social, economic or cultural context of populations), we do not mean that some effort should not be made to adapt to the various situations. It is just as important to solve actual problems as it is to adhere to certain ethical or scientific principles.

The other major discussion, with numerous comments, consisted of certain self-criticism concerning the how and why of research: what is researched, what should not be researched and who should be responsible for the inadequacy or the "uselessness" of the whole set of clinical trials that are created. Placing the guilt on the industry or the market is simply too easy and not always fair. More than one participant insisted that what is called "society", governments, politicians, scientific communities as well as industry or the market rather than industry, is the real one responsible for ensuring that certain research is kept peripheral or delayed *sine die*.

The need to review the dynamics and initiative of where research should begin must be accompanied by proposals on how to correct the dysfunction and imbalance arising. There are reasons and causes, not sufficiently analyzed, for example, that pediatrics, gene therapy, or diseases only appearing in poor countries –such as malaria– are systematically rejected as the subject of research. This issue is unquestionably related to the issue of fair distribution at both a national and international level.

None of these major, complex issues can be conclusively resolved in debates such as this one. However, discussions cannot always be focussed on finding solutions. The contrast between the point of view of science and of ethics is increasingly shown to be more crucial and essential in everything involved in dealing with human life. We could not become aware of this without bringing together perspectives from different professions and kinds of work, joined by common concerns. This monograph is intended to contribute to this unending debate.

VICTORIA CAMPS
CHAIRPERSON

ETHICAL AND SCIENTIFIC STANDARDS IN CLINICAL TRIALS WITH DRUGS

Silvio Garattini

The growth of medical knowledge obtained through experimental and clinical research in recent decades has produced a flow of new drugs. The need to document precisely the benefits:risk ratio for each one has led to a huge increase in clinical trials. Trials in human beings, in the most widely accepted sense, involve new or old drugs for specific therapeutic indications. A lot of water has flowed under the bridge since the days when three doctors' prescriptions were enough to test a new drug in patients. The progress has certainly been made partly because it is now mandatory to follow a clearly-signaled - though increasingly jammed - path.

First of all information must be obtained, through preclinical studies *in vitro* and on animals, to justify investigating the new drug in human beings - or the new preparation of a known drug, a drug combination, new therapeutic indication, etc.

Preclinical studies should provide a rational basis for the possible therapeutic benefits, and reassurance as regards the safety of the new treatment. Without these findings the drug is unlikely to pass muster for testing in humans but once they have been obtained clinical trials can be planned.

Trials are organized in four phases. In phase one the safety of increasing doses of the drug is tested in health volunteers, and its kinetics and metabolism are checked; biochemical effects are investigated to verify the activity established in animal tests. Phase 1 is conducted in actual patients when the drug's toxicity is justified in the light of its therapeutic aim, for example against tumors.

Phase 2 is designed to provide a preliminary picture of the therapeutic efficacy in the indication for which the new treatment is intended.

Phase 3 is the most delicate and decisive stage of clinical investigation. These tests must demonstrate the therapeutic efficacy of the new preparation in comparison with a concomitant control group given either a placebo or the best available treatment for the specific indication.

Phase 4 is an extensive investigation, in a setting close to clinical conditions, aimed at detecting infrequent toxic effects that only come to light in large populations This phase when it is done - comes after the drug has been put on the market.

Another step forward has been achieved with the obligation to submit each clinical investigation phase to an ethics committee whose basic responsibility is to approve the protocol setting out the background, aims and methods of the

trial - suggesting any changes it considers necessary - or to reject it. The ethical committee is made up of scientists and lay people, who must have no material or ideological interest in the trial they are called to assess.

In Italy ethics committees have gained enormous importance in the light of new ministerial decrees that clinical trials can be started - except for phase I, which must still be authorized by the *Istituto Superiore di Sanità* - as long as an ethical committee has approved the protocol.

These committees have multiple, hard-to-define tasks. A pragmatic definition would state that they have basically to protect the patient's interest, in the face of the financial and other interests of whoever proposes the trial. Members thus have to have considerable competence, besides a vigorous spirit of criticism, two gifts it is hard to imagine are universal among the many ethical committees in any country. They are, however, all the more necessary considering that the protocols put forward by the pharmaceutical industry are usually subtly drafted by international specialists.

The first ethical requisite of any trial is that it should provide an unambiguous answer to the question it poses. In other words if a protocol leaves any doubt about the possibility of verifying the potential value of the drug tested, the trial is not ethical. It exposes patients to potential risks without this exposure being useful to them in any way - even a negative finding can be useful - or to the much larger numbers of patients subsequently destined to receive the drug. We must remember that when a drug is approved by the European Medicines Evaluation Agency - EMEA - on the basis of one trial, it can be used by patients in 15 countries with no further national evaluation.

An ethical committee's work involves a certain amount of routine, but there are also quite a few problem areas, calling for reflection.

Under the "routine" heading there are certain key areas indicating the main points of a protocol, which the committee must debate in detail.

1. Controls The efficacy of a drug can never be assessed in absolute terms. Sometimes a group of patients treated before the test therapy was available is proposed as controls - these are known as "historical controls". But how can we compare results obtained at different times, considering the changes that take place in how a disease is diagnosed, or how the natural history of the disease is

influenced by knowledge about the effect of lifestyle habits, or other therapeutic measures? Controls must be contemporaries so that a drug' s efficacy can be assessed comparing exactly what happens in treated and untreated individuals.

Without a control group statistical analysis is impossible so there is no reliable way of checking whether the treatment really benefits the patient.

2. The placebo A placebo is an inert substance given basically to overcome problems of the patient being artificially "convinced", or the often positive effect of the physician's friendly attempts to relieve a disease by giving a new drug, describing its effect and its properties. It is sometimes astounding to see the effect of a placebo. In actual fact this is often just a question of the disease taking its natural course and - fortunately - getting better.

A placebo is not always needed and should not in fact be used, for ethical reasons, if an effective treatment is already known for the disease under investigation. In such cases the available drug must be used as the reference against which to investigate the new compound's properties.

One example: today it is no longer possible to study a new fibrinolytic agent in comparison with a placebo in patients with myocardial infarction, since the GISSI trial (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto) demonstrated with reasonable certainty that streptokinase reduces in-hospital mortality.

The reference drug must be used in conditions in which it is most effective. Doses, administration schedules and routes must all be critically assessed to make sure the new drug has no - even unintentional - advantage.

3. Double blinding This technique has proved very important in clinical pharmacology. The new drug and its placebo or reference drug must be presented so they cannot be recognized by either the physician or the patient. A code can be used, for example, instead of the drug name. This ensures that the patient and investigator are not influenced - however unconsciously - in their assessments of the effects. The code is broken only at the end of the trial, so no-one's judgement is affected.

Many trials have shown that the double-blind method can give quite different impressions from open investigations, but it is not always feasible.

4. Randomization Patients are assigned at random to the group to be given placebo or the reference drug, or the test treatment. Randomization is necessary to ensure that the physician does not assign patients - without being aware of it - on the basis of the severity of their disease or some other criterion to one group or another, thus making any comparison unreliable. Randomization ensures a "fair distribution" so that all patients start out with the same advantages and risks in relation to the treatments.

5. Size of the groups Anyone with the slightest knowledge of statistics will know that the bigger the sample examined the more precisely the difference between two treatments can be assessed. Too small a trial population exposes the investigator and patients to two possible risks: a) they may see an advantage where in fact there is none, attributing an advantage to the new drug that is actually simply a question of chance; b) they may not see an advantage that in fact is there, judging the drug inactive just because the trial was not powerful enough.

When examining a trial protocol, therefore, it is essential to check how many patients it intends to use to draw its conclusions. Small groups are often used on purpose, so as "not to detect" a difference. This happens, for example, with antidepressants, when a new drug is compared with an existing one. The smaller the group tested, the smaller the likelihood of any differences between the two treatments reaching statistical significance. This permits the - inappropriate - conclusion that the new drug is as potent as the existing one.

This is what gives rise to the numerous "me-too" drugs on the market, all in the same therapeutic category. A well-designed trial establishes the numbers of patients needed in each group beforehand, so it knows the power of the study, meaning the smallest difference detectable at a statistically significant level.

6. Parameters for efficacy It is essential when assessing a drug to decide what criteria will be applied for deciding whether the result is good or bad. An opinion on a drug's activity is always based on several assessments - instrumental,

biochemical, behavioral, etc. - but it is fundamental to use parameters that establish how the patient will gain from using the drug. Generally speaking, the gain should involve an improvement in the quality of life or survival; other assessments may be important but less decisive in proving therapeutic efficacy.

The benefit must always be weighed up against the toxicity involved with any drug. Protocols that do not adequately describe the methods to be used for detecting and reporting toxic effects of the test drug should be viewed with suspicion. Equal care should be taken in assessing benefits and risks, to see how they compare, especially when two drugs or two therapeutic strategies are being evaluated.

7. Statistical analysis Statistical experts must be called in when planning a trial, since there is not much they can once it is over. The protocol specifying how the trial is to be conducted must be drafted with statistics in mind. Therapeutic significance cannot be achieved without statistical significance, but the opposite is not always true!

8. Expression of the results Without going into technical details, a trial must be designed so its results are easy to understand and clinically meaningful. Expressing findings simply as percentages may be misleading. The relative risk (RR) should be used, the reduction of the RR, and the reduction of the absolute risk (ARR), and confidence intervals (IC) must be given for these estimates; the number of patients that have to be treated to avoid an event must also be calculated (NNT).

For example, a drug looks different if you say that it reduces mortality by 30% or if you specify that 997 patients must be treated uselessly for a year so that three can benefit. And yet both statements are just different ways of presenting the same findings.

There are three particular problem areas.

1) The discovery of a new drug is usually followed - depending on the size of its market - by a series of analogues. Examples are the first blood cholesterol-lowering agent, simvastatin; the first ACE inhibitor, captopril; the first antidepressant, imipramine; the first non-steroidal anti-inflammatory drug, aspirin; the first angiotensin II receptor

inhibitor, losartan, and so on (Table 1). Some of them offer a small margin of advantage, for example, one dose a day instead of two or three. But for most of them the gain is negligible, and there are no rational grounds to help a doctor decide which of the 18 ACE inhibitors available on the market to use when starting antihypertensive treatment. Normally the choice is based on a "feeling" - a personal impression - usually reinforced by advertising.

These drugs, virtually copies of the original, are known as "me-too" drugs, reflecting the manufacturer's desire to elbow in on the market. This is what raises the question of ethics: is it ethical to approve a trial when one knows in advance, from existing documentation, that there is very little probability of the new product being any different from its parent drug and other analogues?

The argument will go that since there is some difference in its chemical structure the new analogue will be less toxic, or its toxicity may in some way differ from that of the reference drug. If this is the point the protocol should concentrate on confirming these differences. Another basis for approving these trials is that the new product will be sold at a lower price if it proves to be equivalent to the reference drug.

When no specific reasons are provided approval of "me-too" trials poses definite ethical problems. Why should patients be exposed to a "new" treatment when there is no proof that they, or the whole population with that disease, will gain from it?

2) In recent years there has been an increasing tendency to design trials for drugs which are claimed to be superior to similar ones already on sale - a claim usually not borne out by available information - so as to gain approval for studies on small numbers of patients. These trials generally show the treatments are equivalent, but the margin of uncertainty is such that it is impossible to exclude that the test drug is definitely not less active or more toxic than the reference drug.

An example serves to illustrate this point, taken from the "life-saving" category of drugs. Since the mid-Eighties a series of large randomized clinical trials with 20,000-40,000 patients has shown that thrombolytic therapy can reduce mortality from acute myocardial infarction (1,2). The extent of the benefit has fuelled much research for new thrombolytic agents. However, uncertainty about further gains compared to the drugs used so far -

streptokinase and tPA - has suggested that trials should be aimed at demonstrating equivalence rather than superiority. The results are therefore hard to interpret because the efficacy of the new drugs - e.g. reteplase and saruplase - cannot be assessed properly in relation to current thrombolytic treatment.

Equivalence trials give imprecise results, because they are obtained with too few patients – 3,000-6,000 compared to the 20,000-40,000 mentioned for the superiority trials. The confidence intervals are so wide that reteplase, to take one example, may seem to save seven lives per thousand more than tPA, but it may also save seven less. Likewise reteplase may give rise to an excess of 13 patients per thousand with stroke, compared to those treated with streptokinase (3). Similar data come to light for saruplase (4) - see Table 2.

It is obviously hard to accept this sort of "equivalence" which is based on uncertain data and which cannot show the risk or benefit for the patient compared to current treatments. We are talking here about "hard" end-points: death or stroke.

The fact that ethics committees approved the trials brings us back to the need for a critical spirit when assessing trial protocols. The findings also case serious doubts on the ethics of randomization, when it was clear at the outset that the trial could not give definite answers.

A glance through the scientific literature on antidepressants confirms these worries. Table 3 illustrates the so-called equivalence of different tricyclic antidepressants and serotonin re-uptake inhibitors, also used for the treatment of depression. Looking at the numbers of patients, the finding of equivalence may well in fact be equivalent to considerable differences. In many cases it is clear that equivalence trials mask a desire not to find differences !

3) As drugs become increasingly powerful, it becomes harder in certain areas to demonstrate the superiority of one over another, without testing them in such huge numbers of patients that the trial becomes unmanageable.

If we take a disease that has a five per thousand mortality rate, we shall need tens of thousands of patients to show that a new drug is any better than an existing one. To get round the difficulties of such "mega-trials", one solution has been to combine several end-points. For example, in patients with arteriosclerosis, instead of just assessing mortality, the end-points can be

pooled, so that mortality is considered together with myocardial infarction and stroke. With a larger number of events fewer experimental groups are needed.

This approach also poses ethical problems because it risks producing distorted or even misleading information, which may penalize patients - and national health services - when pharmaceutical companies stress the findings in their advertising.

One example will clarify this point. Much interest was aroused recently by the CAPRIE Steering Committee (5), a study that showed that clopidogrel, a platelet antiaggregant drug, was superior to aspirin in preventing morbidity connected to arteriosclerosis. This trial used a combined end-point, like that mentioned above, and clopidogrel proved superior to aspirin (respectively 9553 and 9546 patients in the two groups; 939 and 1021 events; p=0.043).

Though that conclusion leaves no doubt, closer analysis of the findings arouses considerable doubt about the fact that myocardial infarction was improved by clopidogrel, and aspirin seems to have been less active in patients with peripheral arterial disease. The doubt is founded, because these subgroups of patients at risk were too small to provide statistically useful - hence clinically useful - information.

In addition, if the end-points are grouped differently, the statistical significance of the presumed difference in efficacy between aspirin and clopidogrel disappears (Table 4) (5). This happens, for example, if one includes amputation among the measures of efficacy, this being a clinically important end-point in the population at high cardiovascular risk in this trial, which included a subgroup with peripheral arterial disease.

The consequences are now clear of this and other trials that group heterogeneous patients and endpoints. The risk is that patients will be treated with the drug considered to be more active, but which probably is not so for some of them.

As a whole, these points illustrate the fundamental role of ethics committees in ensuring that patients are only admitted to trials in which the likely benefits are greater than the risks. This calls for a much more aggressive spirit of criticism, which in turn calls for sounder scientific thinking.

Milano, February 1999

Table 1

Active principles and products distributed free of charge by the Italian National Health Service.

Pharmacological Class	**No. active principles**	**No. packs**
Cardiac glycosides	1	8
Diuretics	15	38
Antiarrhythmics	7	17
Beta-adrenergic blockers	16	53
Antihypertensives	3	12
ACE inhibitors	18	70
Alpha-adrenergic blockers	2	15
Angiotensin II receptor inhibitors	1	3
Nitrates	4	51
Calcium antagonists	10	99
Sympathicomimetics	1	1
Heparin	2	35
Oral anticoagulants	3	5
Fibrinolytics	only hospitals	
Antiplatelets	2	14
Lipid lowering agents	4	21
Cholesterol lowering agents	4	16
Total	93	458

Table 2
Comparison of fibrinolytic agents

	GISSI-1 (1) ISIS-2 (2)	GISSI-2 (6) ISIS (7) GUSTO-1 (8)	INJECT (3)	GUSTO-3 (9)	COMPASS (4)
Comparison no. per group	SK/control 14.452/14.447	rtPA/SK 44.888/44.420	RETEPLASE/SK 3.004/3.006	RETEPLASE/ALTEPLASE 10.138/4.921	SARUPLASE/SK 1.542/1.547
DEATH no. % events avoided/1.000 ± SD 95% CI	 1.419/1.787 9,8/12,4 25,5 ± 3,7 18,3 a 32,7	 3.787/3.888 8,4/8,8 3,2 ± 1,9 -0,5 a 6,8	 270/285 9,0/9,5 4,9 ± 7,5 -9,7 a 19,6	 757/356 7,5/7,2 -2,3 ± 4,5 -11,2 a 6,5	 88/104 5,7/6,7 10,2 ± 8,7 -6,9 a 27,2
STROKE no. % events avoided/1.000 ± SD 95% CI	 115/112 0,8/0,8 -0,2 ± 1,0 -2,2 a 1,8	 655/500 1,5/1,1 -3,3 ± 0,76 -4,8 a -1,9	 37/30 1,2/1,0 -2,3 ± 2,7 -7,6 a 3,0	 166/88 1,6/1,8 1,5 ± 2,3 -2,9 a 6,0	 22/21 1,4/1,4 -0,7 ± 4,2 -8,9 a 7,6
DEATH or STROKE no. % events avoided/1.000 ± SD 95% CI	 1.491/1.845 10,3/12,8 24,5 ± 3,8 17,2 a 31,9	 4.143/4.180 9,2/9,4 1,8 ± 1,9 -2,0 a 5,6	 288/304 9,6/10,1 5,3 ± 7,7 -9,8 a 20,3	 800/389 7,9/7,9 1,4 ± 4,7 -9,0 a 12,8	 97/116 6,3/7,5 12,1 ± 9,1 -5,8 a 29,3
HYPOTHESIS	SUPERIORITY	SUPERIORITY	EQUIVALENCE (CI < 1%)	SUPERIORITY	EQUIVALENCE (OR < 1,5)

Table 3

Maximum difference between two antidepressants accepted as having equivalent efficacy in controlled clinical trials.

Author	Antidepressant drug	Number	–
Norton *et al.*, 1984 (10)	Fluvoxamine, imipramine, PLO	91	44%
Cohn, Wilcox, 1985 (11)	Fluoxetine, imipramine, PLO	166	33%
Domínguez *et al.*, 1985 (12)	Fluvoxamine, imipramine, PLO	101	41%
Cassano *et al.*, 1986 (13)	Fluvoxamine, imipramine, PLO	481	19%
Lapierre *et al.*, 1987 (14)	Fluvoxamine, imipramine, PLO	63	52%
Muijen *et al.*, 1988 (15)	Fluoxetine, imipramine, PLO	81	47%
Lydiard *et al.*, 1989 (16)	Fluoxetine, imipramine, PLO	54	57%
Feighner *et al.*, 1989 (17)	Fluvoxamine, imipramine, PLO	86	40%
Feighner *et al.*, 1989 (18)	Fluoxetine, imipramine, PLO	145	34%
March *et al.*, 1990 (19)	Fluvoxamine, imipramine, PLO	54	63%
Dunbar *et al.*, 1991 (20)	Paroxetine, imipramine, PLO	717	16%
Shrivastava *et al.*, 1992 (21)	Paroxetine, imipramine, PLO	120	39%
Doogan y Landgon, 1994 (22)	Sertraline, dothiepine, PLO	308	23%

PLO = placebo

Table 4
Intention-to-treat analysis – Primary and secondary endpoints.

Events	Treatment groups	No. events[@]	Incidence events/yr	Relative risk (95% CI)	p
Ischemic stroke, MI or vascular death (primary endpoint)	Clopidogrel (n = 17.636)	939	5,32%	8,7% (0,3%, 16,5%)	0,043
	Aspirin (n = 17.519)	1.021	5,83%		
Ischemic stroke, MI, Amputation or vascular death	Clopidogrel (n = 17.594)	979	5,56%	7,6% (-0,8%, 15,3%)	0,076
	Aspirin (n = 17.482)	1.051	6,01%		
Vascular death	Clopidogrel (n = 18.377)	350	1,90%	7,6% (-6,9%, 20,1%)	0,29
	Aspirin (n = 18.354)	378	2,06%		
Any stroke[+], MI or death due to any cause	Clopidogrel (n = 17.622)	1.133	6,43%	7,0% (-0,9%, 14,2%)	0,081
	Aspirin (n = 17.501)	1.207	6,90%		
Death from any cause	Clopidogrel (n = 18.377)	560	3,05%	2,2% (-9,9%, 12,9%)	0,71
	Aspirin (n = 18.354)	571	3,11%		

from CAPRIE (1996)

n yrs/pts at risk per single groups of events.
[+] including primary intracranial hemorrhage.
[@] only the first events are considered.

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RESEARCH ETHICS IN "DEVELOPING COUNTRIES"

Solomon R. Benatar

I want to begin by referring to what Dr. Garattini said this morning. He has pointed out how the world of medicine in which we work is filled with an enormous amount of useless activity. Of course not everything that is called useless is necessarily useless; it may have some value, but there is a lot of activity that does not produce necessarily what we expect to produce in medicine, and that certainly does not necessarily translate into good health. I will come back to that a little later.

He has also made the point that there are 150 ethics committees in Italy. Anybody who has worked on an ethics committee knows what a complicated job it is. The task goes beyond reading protocols and trying to evaluate them, to include debates in the ethics committee to ensure that all members understand what is going on, what it means to be a member of an ethics committee, what the responsibilities are, and what the role of an ethics committee encompass.

In South Africa, until about 10 years ago, our ethics committees for evaluating clinical trials on human beings were very rudimentary. There was no set standard for how the committees should be structured, how they should operate, what the expectations of the members of the committees should be, and how international standards should be applied in different contexts. In the early 90's the Medical Research Council of South Africa decided that it would produce a detailed set of guidelines for ethics committees. It had previously had two sets, a first edition and a second edition, but these were not comprehensive.

As we did not want to "reinvent the wheel" or write a set of guidelines unique for South Africa, we examined the documents produced by the Royal College of Physicians of London on ethical principles for ethics committees and the international guidelines for medical research produced by the Council for the International Organization of Medical Sciences in Geneva (CIOMS), an organization affiliated to the World Health Organization. We obtained permission from both to use their documents as the basis for a South African version which would include any necessary specifically local features for our own society. In this way we hoped to produce a document which might make it possible for the ethics committees in our various universities and through the country to be encouraged to think more deeply about what they were doing and to have a set of guiding principles which would enable them to understand a set of complex issues. And so we produced this booklet: the guidelines on the

ethics of medical research by the Medical Research Council, acknowledged on the front as heavily based on the Journal of the Royal College of Physicians, and the CIOMS document.

The CIOMS document was only in draft form at that time, and subsequently appeared, in 1993 entitled "International Ethical Guidelines for Biomedical Research Involving Human Subjects". Both the South African document and the CIOMS guidelines are in the process of being rewritten. I hope to play a larger role on the latter because some of the issues that I wish to introduce will strengthen the ethics of research in a document which must be a powerful conscience to insure that the interests of the pharmaceutical industry and of medical practitioners that are increasingly being driven into a consumerist form of medicine, do not become so powerful that vulnerable people are abused.

It is fair to say that drug trials have become a major industry in their own right. In a recent article in *The New England Journal of Medicine* (7th January, 1999) it was noted that the expenditure on drugs has grown faster than the expenditure on anything else in medicine. In 1997, expenditure on drugs increased by 14%. It is the fastest growing component of the expenditure in health care. The vested interest of drug companies in selling drugs extends beyond the small proportion of people in the world to those who are well and hope to avoid disease in the future. So, looking for drugs that will prevent something in the future and having people on those medications for life, is an enormous and powerful industry with great influence on medical practice.

In South Africa, our Medical Research Council, which is the major body for founding medical research, and our medical schools, had a budget a few years ago of about 60 millions South African rands. The drug industry was spending approximately four times that amount of money on research in the country. So researchers were able to tap into the pharmaceutical companies for research money with much less accountability and with many more benefits for themselves, than through formal sources such as the Medical Research Council. So, the power of the companies to control medicine, to control medical practitioners, to drive medicine down the consumers route is clear. The drive towards profits involves a mindset that values the production of drugs that offer only marginal benefits over other existing drugs, rather than attempting to develop new drugs for common and serious disease.

Consider for example the fact that two million people die every year from malaria. Ninety percent of those deaths are in Africa. Ninety percent of deaths in Africa occur in children under the age of five, and the majority of these deaths take place in the first 48 hours. No pharmaceutical company in the world is interested in developing an antimalarial for treating those children. With the discovery of artemasin, which is an ancient Chinese drug used for 2.000 years for treating fever, the World Health Organization, in association with a private chemical company is making suppositories to deliver this drug to children in the rural areas of Africa. It will not require an injection; it will not require a fridge; it will not require oral or intravenous treatment in children who are vomiting, and it is going to be produced for 17ns cents per suppository. But no pharmaceutical company is interested in it, because there is no profit.

Let me now come on to my formal presentation. All I have said up to now has been impromptu and stimulated by our discussion here today and it is preliminary.

I shall begin my presentation today by reminding ourselves of the history of unethical medical research, as we must not forget the past. The record of such research on humans – not only in Germany, but also in the US, the UK, and elsewhere – has provided sobering moral lessons. As history has a tendency to repeat itself, knowledge and discussion about unethical research should be included in the education of scientists.

Fraud, conflicts of interest in medical research and how accusations are investigated have also become increasingly problematic.[1] I draw your attention specifically to a recent article on this subject in Nature[2], and to the book by Kevles on the Baltimore case[3].

My presentation will not dwell either on unethical research on humans, or on scientific fraud, but we may wish to discuss both issues in the discussion period. Suffice it to say that regulation of research and the accountability of researchers remain the subjects of widespread and intense debate.[4-8]

Considerations on ethics and scientific integrity are also relevant to recent debates on informed consent and on HIV transmission studies, which we have raised questions about research in developing countries, and about the application of International Guidelines for Biomedical Research Involving Human Subjects (CIOMS 1993)[8].

World Views or "Mind Sets"

I should also like to make the point at the very beginning of our discussions that we need to understand the framework within which we think and live.[9] Our Western world view within which these debates are taking place is characterized by a biomedical approach to disease, and by neoliberal approach to economics and trade. These are powerful forces influencing the world and need to be considered when evaluating the "dark side" of progress during the 20th century.[10]

Our modern world

I wish to suggest that we need to place our discussions in the context of the world in which we live at the end of the 20th century – a world characterized by widening economic and health disparities between rich and poor (within and between countries), by a massive arms industry, many wars, excessive human conflict, socially caused suffering, the displacement of millions of people from the homes and cultures which are vital to sustain their self respect, and new epidemics of infectious diseases. We thus need to ensure that our thoughts are not constrained by a narrow perspective on such complex problems.[10,11]

At the beginning of this century the ration of the richest 20% of the population to the poorest 20% was 9:1. By 1960 this ratio had widened to 30:1, by 1990 to 60:1 and by 1997 to over 70:1. About 1.3 billion people live in absolute poverty – more than ever before - hungry, suffering unnecessarily and dying prematurely. Do we understand what the world looks like to those who live in misery? Do we have the insight into how the practice of modern medicine and how we as elite researchers are viewed? Inequities at the global level mirror the disparities engendered by apartheid in South Africa. The world was correctly horrified by the exploitation that took place in that country. But South Africa is a microcosm of the world, and the same exploitative forces which created wide economic disparities in that country are also operative at a global level.

A good case has been made by scholars from the London School of Hygiene and Tropical Medicine for global health and AIDS to be seen in the context of the global political economy and its exploitative ideology.[12] A system which has polarized people so profoundly, provided them with only marginal benefits

of progress and consigned them to terrible living conditions – without access to clean water, inadequate sanitation and access to only rudimentary health services - has allowed diseases such as HIV/AIDS to arise and flourish. Third world debt and the processes through which this has been created and sustained are central factors in maintaining impoverished lives. If these scholars are correct in linking the global political economy to the emergence of new infectious diseases, other dreaded diseases may arise in the future. This should be born in mind when we are faced by the haste of scientists in wealthy countries to test new drugs for AIDS and to produce an AIDS vaccine. We have the means to treat tuberculosis and to eliminate measles and yet these diseases are rampant. Having a vaccine against HIV will not eliminate AIDS or even reduce the magnitude of the problem if we use this as ineffectively as we use anti-tuberculosis treatment and the measles vaccine. Health is about more than drugs and science.

The need for more than science - a higher profile for ethics

Science is necessary for human progress, but it is not sufficient on its own to ensure human flourishing. Scientific advances must continue and science should receive maximal support. It must also be born in mind that science alone will not solve the problem of infectious diseases and other causes of poor health. Attention to the broader issues I have alluded to above is essential.

Ethics has received only minimal attention in South Africa and in many developing countries. Resources have not been made available to develop the expertise and infrastructure required to evaluate ethical problems, to educate practitioners and researchers and to facilitate the development of defensible public policies. To be able to understand, promote and advance science requires scientific training and expertise. To understand and deal with ethical dilemmas requires similar levels of scholarship. This academic field of endeavor, and its application to practice, cannot be adequately dealt with by those whose insight is restricted by lack of formal training and who have only a superficial understanding of the complexities of the subject.

Research ethics committees – brief review of functions

Scientific merit

In evaluating research protocols their scientific merit is the first aspect which must be evaluated. Here the focus is on study design, methodology and analysis – as described by Professor Garattini.

Ethical merit

Evaluation of scientific merit must be followed by a rigorous evaluation of the ethical merit of the intended program. Essentially this is about protection of the dignity of research subjects. It must be recognized that there is the potential for all research to be exploitative, and exploitation of research subjects must be avoided. Ideally the focus of researchers should be on the internal rewards of research – the pursuit of knowledge and truth. While the pursuit of such external rewards as money and fame cannot be avoided excessive emphasis on these should be counteracted by careful attention to due process and accountability.

Ethics committees have several potential functions – reviewing, educating, and auditing.

Reviewing ethical protocols is a well-developed and implemented task, which consumes most attention. The ethical review/evaluation of protocols should cover several issues:

(i) assessment of the risk/benefit ration of research,

(ii) assessment of the degree of *equity* in distribution of benefits and burdens,

(iii) evaluation of whether adequate *information* has been provided for subjects, and

(iv) ensuring that various attention has been paid to protecting various *freedoms*:
freedom of consent,
freedom of withdraw (without prejudice to care), and
freedom to publish,

(v) review of aspects of *payment* to research subjects – excessive payment that may amount to coercion or taking undue risks to participate must be avoided.

(vi) *ensuring the provision has been made to compensate* research subjects (by the sponsors of research) for any damage that may result in the research study.

(vii) Seeking *and eliminating conflicts of interest*

Such conflict at the individual level includes conflict between the role of the clinician (who should be concerned only with the well being of patients) and the role of the researcher (whose predominant concern is for the advancement of knowledge), especially if the investigator is also the researcher. At the levels both of individuals and of institutions there is a need to be aware of sponsorships, power struggles, secrets and the quest for fame which may prejudice research subjects for the benefits of researchers or institutions.

(viii) *confidentiality*, and the means of *data dissemination* also need careful scrutiny.

The reviewing function of ethics committees needs to be supplemented by two other roles neither of which are well developed and practiced but which need to be expanded in order to buttress the review function:

Education of researchers. Researchers need to have a broad education, which includes insight into research ethics and the responsibilities of scientists. These considerations have been clearly spelt out by the US National Academy of Sciences' publication "On being a scientist".[13]

Audit of how research ethics is carried out. It can also be argued that ethics committees have a responsibility to audit such actions as how informed consent is obtained by researchers in practice. Unless this is undertaken there is no way of knowing that what researchers say they will do is being done!

Research ethics in developing countries.

Several considerations are relevant regarding research in developing countries:

– the *heavy burden of disease*, (particularly infectious diseases);
– the breath and depth of *poverty*;
– the level of *illiteracy*;
– the extent of *disempowerment* of the poor in their personal and communal lives;

– the *lack of an infrastructure to review research and research ethics*;
– the *gap between the understanding and motives* of external funders/researchers and local institutions/researchers and the *expectations of local researchers/patients.*
– the *need to improve the lives* of the vulnerable and disadvantaged and
– the need to *ensure that when research is undertaken on the vulnerable the beneficial results can be made available to them and others in poor communities*
– the need to avoid *exploitation*, through selective ownership of data and its use – including the problem of intellectual property rights.

In the past few years some key questions have been directed at the ethics of research. The first relates to whether informed consent is always necessary, and to how it should be obtained. The second relates to the use of placebos. Both these issues have been of special importance to research in developing countries and have raised the question of whether guidelines such as the Helsinki Declaration and the CIOMS guidelines can be interpreted universally or whether there is any need for contextual modification in their application.

With regard to informed consent

(i) It is generally agreed that this is always necessary – except in very special circumstances where good reasons can be provided and alternative acceptable practices are legitimately in place.

(ii) There is also a need to consider *different understandings of what it means to be ill* and of what can be expected from those one consults for help.

(iii) Similarly there is the need to consider *the way in which Africans and members of other communities traditionally view themselves* as individuals embedded in their communities (with due consideration for heterogeneity within countries and changing boundaries between different cultural perceptions of the self).

These considerations have relevance for informed consent and how this can best be obtained with due regard for respect for persons as they see themselves, while simultaneously seeking to *empower* them to become more autonomous. Special care is thus necessary in obtaining informed consent when language and cultural differences separate investigators from research subjects.

In recent debates about HIV transmission studies in Thailand and South Africa questions have been raised regarding the use of placebos, and the extent

to which absolute clarity can be provided on precisely what is ethical in research by a guideline such as the Helsinki Declaration. In response to these issues it should be noted that somewhat dogmatic ethical prescriptions have been summarily delivered, and inappropriate analogies have also been used – for example comparing the Tuskegee researchers and their respective ethics committees. Such superficial and inaccurate analogies do a grave injustice to the review process, cast aspersions over the best intentions of researchers, and disregard the implications of these studies for the local populations.[14]

It would also seem simplistic to imagine that the legitimacy of using a placebo arm can be determined solely on the basis of an all-encompassing rule, or to consider that all the ethics of research can be deduced from such guidelines as the Helsinki Declaration. Guidelines are not intended to cover every possible circumstance and, like laws and constitutions, require interpretation.

Thus it cannot be assumed that a particular drug regimen, considered to be the best standard treatment in one situation, is necessarily the best in another. Whether or not a particular drug regimen can be considered the best standard or whether a placebo arm is ethical will be determined by such issues as: (i) the strength of evidence that any treatment has been shown to be superior, (ii) the ability to extrapolate the results of drug treatment in one context to another, (iii) whether the drugs can be safely delivered in a radically different environment, (iv) whether the study is being done primarily to benefit to local population, and what study design can best achieve this, and (v) the implications of the outcome of the study for the subsequent implementation of a national policy to make the new treatment available to the community.[14]

For example, in the HIV transmission studies the best "proven" drug regimen would have had to be given for 14 weeks prior to delivery, intrapartum, and to the infant for four weeks, in the absence of breast feeding – an almost impossible combination for most women in developing countries who present a only a few weeks before delivery and whose infants would be placed at considerable risk if not breast fed. The use of a placebo in such situation can be justified, especially as the standard treatment could not be a feasible option, because of expense.

If it is insisted that the best standard drug regimen must be used it can also legitimately be asked why ethics limits consideration to the best available standard drug treatment. Why not include the best standard medical, nursing

and hospital facilities? If expense is not a consideration for drugs why should it be for other aspects of treatment?

I am suggesting that good reasons can on occasion be provided for structuring studies differently in different contexts without having to accuse researchers of moral relativism. An imperial or dogmatic mind-set may obstruct access to the fact that it is often ethical considerations, which require that such studies be structured differently. Achieving universality in ethical standards requires reflection on: what constitutes the best interests of subjects, and what distinguishes truly universal from imperialistic conceptions.

It is also necessary to ensure that research and external intrusion will bring significant benefits to the research subjects and their community. Further it is justifiably argued that given the record of past exploitation and indeed its ongoing practice, external researchers have an obligation to ensure value to the host community and to use the research process to empower local researchers and subjects to become more independent.

Conclusions

Making scientific and moral progress requires:

- the ability to be skeptical of the current status of knowledge, method and dogma;
- the willingness to raise critical questions on any issue; an understanding of one's own framework of thinking (in our case a mind set characterized by *a biomedical approach to disease/neoliberal approach to economics and trade*);
- the humility to recognize that one's own insights are not necessarily correct or better than those of others,

A willingness to debate differences with an open and scholarly attitude is an essential feature of any rational ethical approach. Debate on these issues cannot be undertaken solely within industrialized countries, and must include members of developing countries.

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DISCUSSION

Carles Vallvé. I have taken the liberty of speaking first because I think I belong to the richest quarter of this population group, at least in terms of life experience! Two options have been introduced this morning. One option has been proposed by Prof. Garattini, in which clinical research is required to adhere to the highest possible ethical standards in order to protect the integrity of patients involved in clinical trials. Prof. Benatar has also suggested something very interesting by discussing the ideas of Robert Levine, if I am not mistaken, concerning a physician who treats patients and a scientific physician who is responsible for the high standards of the methods used in clinical development. These ideas in which two physicians are actually responsible for a clinical trial are really not practical but are reflected in the current clinical research ethics committees.

Prof. Garattini has also requested or proposed that the clinical research ethics committee be the instrument or safety valve for all experimental activities performed on humans.

Therefore I would perhaps like to stimulate the discussion somewhat (as I am aware that there are colleagues here with considerably more experience than myself in the tasks involved in ethics committees) by stating that, in my opinion, ethics committees have failed in their mission on the whole. The ethics committees only partially protect the patient; instead they basically protect the interests of both the physicians and institutions they serve. As far as I know there are no independent ethics committees. There are only ethics committees that are part of an institution, and such institutions are generally associated with the pharmaceutical industry and belong to an economic sector of great importance, as stated by Prof. Benatar.

According to the latest reports available, the failure of ethics committees is clear, particularly in the United States. In the U.S. there are not 600 committees (which would be a number comparable to Spain or Italy). There are actually 2,000 clinical research ethics committees. In fact, governmental offices have lodged formal complaints stating that these committees are able to make decisions on complex protocols in just a few minutes. These committees are capable of reviewing 200 protocols in just one session and analyzing up to 2,000 protocols every year. However, this is not the situation in Spain, where the burden of having to perform the scientific analysis of protocols in large hospitals is the responsibility of one or two individuals at most. Generally speaking, these individuals have insufficient resources and are under enormous pressure. Often

the committee chairs are the actual hospital directors. I feel that physicians, hospital directors and health authorities, etc. are also responsible for the current situation of clinical research. I do not wish to become involved in a jeremiad, but all these problems must be brought out into the open so we can improve our efforts from the ethical and scientific standpoint in the field of clinical research.

Fernando García Alonso. I find it hard to say that ethics committees have either failed or succeeded because as far as I know, they are not assessed. This would be the first point: ethics committees are not evaluated and there are only opinions on them. Simply bearing in mind an area we are familiar with, in Spain it would be unfair to say that the committees have failed. We do not have independent ethics committees in the sense described by Dr. Vallvé. The ideal, utopian community of debate described by many philosophers would be required. This sounds fine in a book, but it's not really practical.

In my opinion, the committees in our hospitals have dramatically improved their way of working in the last ten years. In fact, when comparing from a methodological and ethics perspective the quality of the clinical trials we conducted ten years ago with what we achieve today (perhaps the only output we can measure) the situation is reasonable, although still not remarkable.

My basic opinion is that in Spain there are a number of problems regarding the issue of clinical trials that ethics committees must improve. The issue should be brought out in the open and discussed, although I do not feel it is one of the most important priorities for us. There is a high level of awareness and excellent professionals and we should now be in the process of doing the same as in Italy. In other words, the idea is that next year in Spain we should work on decentralization (in less than one year it could be achieved) to ensure that decisions on clinical trials are only made by the committees without any referendum by the health authorities being required. In my opinion, we are at the point where we could achieve this high level of development. Nevertheless, I would be very interested in learning how others feel about whether or not this would imply any hazards.

Xavier Carné. After this morning's presentations, which have discussed very critical aspects of the clinical research system currently being carried out in the West and, particularly, in Spain, I share many of the concerns expressed here. My main concern, however, is to contribute something that could change

the situation. In this sense, I agree to a large extent with the ideas expressed by Dr. García Alonso, in the sense that reviewing how the committees operate is important. Please allow me to say, however, that this is not the most important issue at the moment, based on the scenario presented. One key aspect that we are neglecting is that, as Prof. Garattini has so adeptly expressed, at least ninety per cent of the clinical trials in the south of Europe are sponsored by the pharmaceutical industry.

Randomized clinical trials –as I think everyone agrees- is the best clinical research method available and the most robust and resistant to bias.

In Spain there are no organizations resembling the Istituto Mario Negri in Italy, the INSERM in France, the National Institute of Health in the United States or the Medical Research Council in the United Kingdom which are independent public institutions separate from the pharmaceutical industry that which sponsor their own clinical studies under conditions where there is no possible financial interest. This gap is partially bridged in some countries but in our country it is a completely neglected. This cannot continue. Our community must do something so that the best methodological tool is not left in the hands of an industry that, moreover, complicates it with standard operating procedures, good clinical practice, etc. They complicate it so much that an independent group finds it almost impossible to achieve the quality standards, with the proper review and control that is now required.

As a result, I feel our main priority in this field is to develop some kind of system to promote, perform and carry out clinical trials from an independent standpoint of industry, in a non-profit making manner. This is a very important issue still pending in our country, which in my opinion must be dealt with just as in many other countries around us.

Ramon Bayés. Along the same lines as that mentioned by Dr. Carné, I would like to say that perhaps there should be preliminary research and a debate stage to establish the priority for health problems that, regardless of the financial profits or losses obtained because they are solved, are of vital importance for any community. Which of these problems are not tackled by the pharmaceutical industry but still require a solution because they affect the integrity or survival of certain members of society? Who should be responsible for finding a solution? What resources should be available to them?

Fernando de Andrés. I feel the same way. In my opinion, regardless of the fact that scientific standards of research can and should improve and regardless of what must be done to improve them, the basic problem from the community standpoint is precisely what research is being done, i.e., what questions we should raise when we conduct research. I feel we are sometimes pressured to ask the wrong questions.

I would like to mention the problem of AIDS treatment raised by Prof. Benatar. About ten years ago there was only one drug, AZT, which required lifelong use. However, this was the case only a short while because it was used on patients who were about to die. We must now use at least three drugs that are much more costly. These drugs must also be taken for the rest of a patient's life, but now these patients are living much longer. The pharmaceutical industry is seeking more and more new drugs to treat AIDS whereas, in fact, the best solution would be to create a vaccine. Of course, if a vaccine were available such as the ones we had for smallpox, the drugs to kill the AIDS virus would not be needed. The fact that an AIDS vaccine is being developed in Prof. Benatar's country by public institutions and not by private industry is symptomatic.

Victoria Camps. Summarizing the previous comments, I would like to make two observations. Ethics committees have been mentioned and I feel this is a general topic that deserves some attention so we can then go on to consider more specific issues. Based on this morning's presentations on bioethics, I would not say that ethics committees have failed. The ethics committees have implied an important step and there has been progress in the committees. Awareness has increased in all sectors, particularly regarding a fundamental principal which consists of bearing in mind that science and ethics are not two different things. Rather they both involve implementing a good project and a good scientific protocol is one of the primary ethical requirements. The other point is to remember that the patient is a person with their own independence and freedom. Therefore, we must ask for their consent and keep in mind their self-respect.

In my opinion, however, there is something still missing from the ethics committees which is fairness: equitable justice within a given society or given country. This issue is related to the independence of committees mentioned by Dr. Carné. In other words, it will be very difficult for the financial lobbies of industry (which is the sector obtaining the most benefit from the trials) to be

compatible with the principle of fairness until independent committees exist. Moreover, I would like to stress the issue that I think Dr. De Andrés and Dr. Bayés have raised, i.e., that the most important thing is precisely what research is carried out. In other words, whether research is actually carried out for the benefit of the community. This is largely related to one of the first issues raised by Prof. Garattini when he said that, "a great deal of pointless research is carried out". The committees do not broach this question on whether research is useful or not, they only oversee whether the trial is of merely commercial interest, but nothing else. Here there is no opinion that could have an effect on whether a certain trial is accepted or not. Finally, in relation to this issue of equitable justice within an international scope, I would like to ask Prof. Benatar a question. He has talked a great deal about inequality regarding both worlds, and in this respect I would like to recall something Bertol Brecht said, something that has been very much quoted: "We must first eat then we can talk about morality". Taking this into account, I would like Prof. Benatar to tell us how this statement by Bertol Brecht can be applied. Should bioethical principles be inverted and justice be given top priority in the developing world? Perhaps our principles should differ when we talk about informed consent and a patient's independence in a country where the majority of the population are illiterate, unable to read and write, cannot receive knowledge. I do not know whether we can talk of universal principles that can automatically be applied to all countries.

Margarita Arboix. I feel a bit like a fish out of water because, as you have seen, I am involved in the field of veterinary research. Actually, the greatest problem we have faced in recent years is that we have also realized the need to have ethics committees which clinical trials carried out on all kinds of animals, particularly, on animals used for food production because these drugs are often passed on to humans when they consume the food.

You have all seen that the problem of hormones that has come up again. Apparently b-estradiol is genotoxic, etc. What is the problem arising here? When a clinical trial is approved or rejected and when research groups work on products such as growth stimulants, there is always some doubt as to the risks and benefits, as stated by Dr. Camps. What would we consider to be the "target" group when we evaluate the trials? Developed countries have a surplus of many items -milk, meat, etc.- but there are millions of people who do not have enough to eat. The aim is to increase the weight of an animal to obtain a greater volume of meat, something that could mean 20% or 25% more meat

for developing countries. How should we interpret a probable risk of consuming a residual drug over time (although not proven)? How can we decide whether a trial is ethical or not, depending on whom it is to be carried out for?

Francisco de Abajo. I would like to bring up the question of social usefulness again and whether the committees should assess clinical trials that are submitted, basing their assessment on criteria related to social usefulness. When stated this way, it sounds easy. Moreover, I think it is a rule stemming from the principle of fairness and that all committees must endeavor to apply. However, it is not easy for a committee to define what is socially useful or not. It is easy for a committee to decide about whether or not the clinical trial being submitted is scientifically appropriate and about whether or not it harms the interests of research, but this is in fact a very complicated matter.

Personally I would like the information I receive to be empirical data and not merely a subjective impression, for example this morning it was mentioned that 80% of research carried out is of no value. It was also mentioned that bioequivalence research is not socially useful, but I still wonder whether this statement can be sustained because they eventually result in medications that improve upon the base medicine. A decision on social usefulness is too great a responsibility to place upon a committee that does not have the perspective required to make this kind of decision. The ones that should decide on social usefulness are the agencies funding the research and these are the agencies that must decide on the priority for research lines that are useful for society. If we allow a committee to decide whether research submitted by a private sponsor will eventually be beneficial to society, we are putting the committee in a situation I feel is not appropriate.

Silvio Garattini. Well, there has been a number of problems, that have been elicited in this discussion. First of all, I believe that the concept of an ethical committee is extremely useful. There is no doubt that to have an ethical committee is much better than not to have an ethical committee in judging the efficacy of protocols of clinical trials. So, I believe that, even if I agree on the fact that the ethical committee has not been able to prevent useless type of research (there is no doubt on that), there is no doubt also on the other aspect, that without the ethical committee, the situation would have been worse. I think that the real problem is how we improve the situation and the activity of the ethical committee.

But, there is not only the ethical committee; there are a number of factors that should contribute to improve these clinical trials, which are in a way linked but not only related to the ethical committee. For instance, if a hospital puts pressure on his physicians in order to obtain incomes derived from clinical trials, obviously, this is a factor than can be changed, and it is not the responsibility of the ethical committee. Before the ethical committee there is the personal responsibility. Any study has a principal investigator. The principal investigator should be also a responsible person, not to accept type of trials that do not look of use for the community. Here is also a responsibility. He is not an irresponsible person that takes something and brings it to the ethical committee. He has to decide first of all if it is worth or not to perform, and then there is the ethical committee.

The ethical committee, I believe that it is a body that has to learn how to do things. In my opinion, what we have been lacking in this period of time, during these years, is to have courses in order to educate the ethical committee to do well their jobs. In Italy, I do not remember any course given to members of the ethical committees. This could be an extremely useful exercise: to teach to the ethical committees problems, in the way that we have done today, for instance. If the culture increases, certainly there will be an improvement also in the judgement.

There are other things in my opinion that will improve the situation of clinical trials. Some have been mentioned but it is worth to repeat them, for instance: when a scientific journal publishes a paper that is questionable from the point of view of the scientific design (which implies ethical aspects), there are relatively few people who write to the journal in order to make clear which are the points which are susceptible of being improved. I think that if scientific community was be more prone to criticism of what is not acceptable, then automatically the quality would improve.

There is also another thing that has been mentioned and that in my opinion is extremely important: the society (and this is also one of our tasks as a scientific community) should not delegate only to pharmaceutical companies the responsibility to carry out clinical trials. Obviously, pharmaceutical companies have done a lot of good things. Nobody denies that they have done many good things when they have discovered important drugs which have improved the treatment of diseases, but what is wrong in our society is that everything is delegated to them. What we should do is to take action and to do

whatever we can do in order to establish at the national, and particularly today, at the European level, independent funds to support studies which are of interest to the community. I hope that in the discussion we will see which are the major requirements, what we mean by these independent studies which are important for the community. These are studies that are of no interest to the industry, because they do not bring any additional income, but they are important. I will just mention one aspect. Try today to get a grant to study any new activity of ACE inhibitors. It is impossible, because they are going out of patents. They will be generics and the pharmaceutical industry is not interest in spending anymore any penny. Because, if we find something useful, everybody coming up with the generics will utilize this indication. This is a very important example of opportunity to use these drugs for different indications. Theoretically there are many of these opportunities that are not utilized because of economic interests. I think that it will become crucial in the future to have available independent funds, and on a competitive basis, that could be assigned in order to carry out research. I think Dr. Carné said clearly that there should be research with no aim of profit. Clinical studies unfortunately are relatively expensive if one wants to do a good job. Therefore, these funds should be substantial. Otherwise it will be impossible to carry out independent studies. Thank-you.

Solomon Benatar. I would also like to respond to some of the questions that have been raised this afternoon. The first point I want to make is to reinforce what Professor Garattini said. I think that the ethics committees have not been a total failure. Yes, certainly, they have not achieved as much success as they could have achieved, but we should accept that the ethics committees that we have are probably better that no ethics committees. But the challenge for the future is to educate the members of the committees to improve the ability of ethics committees to function adequately.

Secondly, I want to support the idea that in any particular county, there is a need for responsible public bodies of some kind, like for example Medical Research Councils, that will set the tone for what kind of research is required in the country. Let me give you an example. In South Africa, in the apartheid era, most of the research sponsored by our Medical Research Council was laboratory-based research done by scientific workers trying to compete with the world to make new discoveries. During the past ten years the Medical

Research Council in South Africa has increasingly allocated up to 50% of its budget to what it defined as essential national health research, to be directed towards those issues which were of special interest to diseases within our own nation. So, they encouraged research workers to shift their direction away from "blue-sky research" of the laboratory, towards some of the challenges facing public health of the country. There is now a much greater emphasis on the illnesses of the marginalized people and on epidemiological research to understand the distribution of disease and what could be done about them in the country. This new focus did not diminish the scientific research because many other bodies began to provide money for basic research. The MRC could thus develop priorities regarding national needs. This means that the ideology of research is not driven entirely by pharmaceutical companies, or by doctors, or by the marketplace. There is also a thoughtful social policy, which attempts to identify what the country actually needs.

That brings me to the next point, and that is that to some extent, and I think it is true, the medical profession has been criticized, as being a somewhat silent profession, not talking enough to patients and not communicating sufficiently with the public. The idea is developing slowly in many parts of the world, that democracy consists of having a dialogue with the community at large, so that debates can be open with the public on issues regarding what they consider to be priorities that do need to be addressed. Of course, it is very difficult to tap into more than a very small proportion of the public, but by making the debate public, by entering into what has been called a deliberative democracy, deliberation and discussion with the public, it is possible for activists within society to turn scientists' thoughts towards issues that should be researched even if the scientists themselves might not have directed themselves towards those issues. I think that the idea of democracy, the idea of hearing the voices of those who are ill and who want research to be done on issues that are important to them, is an important component of being ethical in a society.

Dr. Camps raised the issue that insufficient attention has been paid to justice. And I want to emphasize that point. I think that since the rebirth of bioethics in the United States and throughout the world in the last 30 or 40 years, most of the debate in ethics has been at a micro level. It has been at the level of the doctor-patient relationship. And it has been at the level of who should have power. The shift has been away from paternalism towards autonomy, a shift away from the beneficent doctor who knows best towards the

doctor who is willing to listen to the patient and hear the patient's view. This has been a major power struggle at a micro level. There are two other levels at which justice has to be considered. One is the meso level or middle level, the ethics of how institutions operate. What ethical guidelines should determine how an institution operates? How does an institution allocate its resources? Does it, for example, give enough resources to research on the care of the aged and the children, as it might do for middle-aged people suffering from a particular group of diseases. How does an institution look at itself as an institution and avoid becoming a tyrannical body run by bureaucrats who have a particular mindset about how to manage an institution? How do we examine the ethics of justice in institutions and of health care systems?. What is required within a health care system to make it a reasonably just health care system? Many would argue that an entirely marketplace system is just because it operates according to the rules of the marketplace. Others would say that the total freedom of the marketplace overcomes the needs of those who do not have a voice. It is appropriate here to quote Isaiah Berlin: "total freedom for the wolves is death for the lambs".

There is also the question of the macro level of justice. What should be the ethical rules that guide how nations behave with each other? If money is going to be lend from one nation to another, how should that be accounted for? What process should be followed to track how money is lent and spent? There is a need for accountability at a macro level, to be sure that powerful forces do not control resources in an arbitrary manner. Democracy centers on governments that can be elected in, and removed from power by their citizens. However the power of transnational corporations is unaccountable. They control vast sums of money and yet nobody can elect them into or out of power. The justice debate needs to come back to the macro level. The concept of what does it mean to be just cannot be confined to the doctor-patient level. It also needs to be consulted within institutions, at a national level, and in relationships between countries. This is a neglected debate, and I anticipate that such considerations of justice will become a much more important issue in the next twenty or thirty years.

Finally, let me just come back to the issue that was raised by our veterinary colleague. There is a great deal of concern at the moment, especially in the era of genetic engineering, that there may be all sorts of things that we are doing to animals and to plants which may have implications into the future that we do not understand. Let me give you one example.

The genetic engineering of some basic foods which are resistant to certain forms of pesticides may make it possible for some companies to have a total monopoly on the sale of particular seeds and the pesticides that can be used to control the pests in those environments. The possibility arises of control over the patterns of subsistence production in the world by large corporations. There are enormous implications here for the poor.

The need for ecological sensitivity and the need to understand the responsibility of manipulating DNA, it also makes it very important for us to think about those issues that relate to animals. What might happen if we create transgenic animals? It is impossible that animal infections might be propagated in humans? These are crucial issues to debate.

Francesc Abel. I would like to put forward some ideas. Prof. Benatar has expressed my exact thoughts on this matter and I feel we must be stimulated by the same ideals and inspired by the same spirit. I am in full agreement with most of what he has said, although I am not as sure in my opinions about genetically modified plants and animals.

I would like to mention certain aspects. In my opinion his three-divisional level of macroeconomic, macrosocial, mesoeconomic, mesosocial and microeconomic, microsocial levels was very interesting. I do not feel we are in a position here to deal with the problems referring to justice in the world, although this is an issue which certainly affects all of us. Naturally we must deal with production problems, power consumption problems, pollution problems and all the inequalities in which we can see that the health aspect plays an important role, but this is not everything. At this level I think we can only progress with difficulty except by stating that there is indeed great injustice in the world, and that the resources are allocated in a drastically unequal way.

On a meso level, I do not know whether we can either influence anything or not, although I think we could say something else regarding this. At the microeconomic, microsocial and perhaps on a health policy level, I am sure something else could be said. I will express my opinions on some things that have been mentioned. I think that the clinical research ethics committees, at least as far as I am aware in Spain, have not failed completely. Whereas some time ago the norm was to approve all protocols, this is no longer the case. At least in the pediatric hospital where I work, we have a problem when trials

must be returned because they are below standard. We are lacking serious co-ordination work at the state level. In fact, when a project comes from a multinational firm and certain observations are made precisely because we are dealing with children, how should we convey the fact that we have decided not to accept the project at our hospital? This is a serious issue that we face. We should also mention that I think a great deal of industry does indeed provide benefits, here I am sticking my neck out on behalf of industry. Industry tends to listen to observations that are generally well founded, then to rectify their protocols. Perhaps this occurs because there is a great deal of fear in anything that could imply serious accidents as far as children are concerned. This is another thing that I have also realized. In this sense, I certainly regret that there are, to a certain extent, isolated specialties, such as psychiatry. I think that here risks must be accepted depending on the relatives and even the patients themselves. Indeed, I would not be so hard on the pharmaceutical industry in this respect, but rather on all it represents, i.e., this neo-liberal economic approach present in all aspects of our society. At a level that impresses me enormously, I would covert this into certain very specific questions.

I fully agree with the statement that money is being invested in new medicines for AIDS instead of finding a vaccine. However, I feel this is a political problem right now. Nobody dares to place limits and say we've got to stop using this approach. When the Food and Drug Administration decided to lower the protection levels in terms of clinical trials to go directly to patients with a so-called "compassion drug", I wonder if they have not actually done a great deal of harm because this was an immediate invitation to seek new products. As a result, the costs of treating AIDS is increasing and, in the cases of very small children, it is actually frightening. However, the clinical physician should not be the one who tells a person, "We have to reduce costs and, therefore, we are not going to do what the scientific community considers appropriate at this point just so this child can maybe live a few more days." The managers should call the Health Council or Ministry of Health and asking, "Is there anything we can do to limit these costs if they are not going to provide certain benefits?" This idea of limiting the slender economic resources actually implies –and here we have the element of fairness– that we stop using them for other kinds of patients on the short and long term. This is politically unprofitable and people are afraid of that.

Indeed, I can give my opinion on this because I have been involved in some of these issues. Often you reach a point where the person who has the capacity to make decisions is either not convinced or does not want to make a decision, and the one who is convinced has no decision-making power.

I agree with Prof. Benatar on some of the things related to designing these ethical criteria as a support for certain conclusions that could imply delegation by countries in Sub-Saharan Africa. Several problems that have arisen, for example, apparently it was Great Britain that found itself in possession of some contaminated blood samples that could not be used in Great Britain itself. The question is should they be sold to Third-World countries at a lower price such that the blood would save many lives, even though there might be some more cases of AIDS? There are two opposing points of view. A "yes" answer would certain problems or a "no" answer would create other problems. How do I react with my western mentality? It find it appalling. How would people affected by this problem react? I actually am unsure. However, something curious I learnt at our meeting was that this problem was considered (please correct me if I am wrong) to be relatively peripheral in comparison to another problem, namely, why does the Western world generally feel that clinical trials carried out in the Third World require lower investment levels? The actual investment level should be higher, but perhaps employed in another way. This greater investment would imply assisting in the cultural development of the population. First, the local doctors themselves must understand the importance of vaccines; then the village chiefs should be educated on this matter as well, thereby making it necessary for only a small amount of government pressure to get people to actually visit the doctor.

Another issue concerns the clinical trials carried out in areas affected by malaria (Tanzania, among others). I would like to learn the opinion held by people who have worked on these trials, myself being among them. I would specifically like to ask Dr. Alonso to tell us something about this. In terms of those referring to AIDS, I have huge problems regarding this in Africa and would like to gain some insight on this aspect rather than on how we are going to solve the world's problems. This is my opinion.

Fernando de Andrés. My comments are not general but specifically refer to common themes and are more along the lines of supporting Dr. Carné's

remarks rather than attacking industry. I cannot complain about industry. Industry does what it's supposed to do very well. Many times it doesn't do something simply because that's not part of its job and it shouldn't being doing it. My complaint is limited to those who *should* do something but don't do it. They only judge, criticize and regulate what others do instead of taking the initiative themselves. This is a key point. Naturally the anti-retroviral pharmaceuticals are very welcome, as they are improving the prognosis for AIDS. I do not know if we are of the same opinion, but I rather agree with the FDA, which has avoided bureaucracy so as not to delay these pharmaceuticals appearing on the market. The EMEA (i.e., the European Agency) has also done the same thing. Prof. Garattini is well aware of this fact. Since industry does not do everything, feels a significant amount of pressure and is motivated by its own concerns, my complaint is that someone must do it. Some system must be found so that other people, other bodies, other parts of society take the initiative. My comments are basically heading in this direction.

Pablo Díaz Villoslada. I would first like to mention that public interest in research must be co-ordinated at a national or perhaps European level by national research agencies. I am unaware of whether or not the Health Research Fund could give us an opinion on this. Moreover, as mentioned by Dr. Carné, there are difficulties at present in trying to develop clinical trials that are not funded by agencies. When we try to test drugs for common use such as, in our case, corticoids, endeavoring to avoid intravenous administration by using oral administration, it is extremely complicated to find funding for clinical trials involving a low-cost medicine. I have seen that Hospital Clínico is also trying to test heparin to prevent stroke, and encountering inherent difficulties to conduct this kind of investigation.

Basically I would like to contribute from the standpoint of an investigator, as only the ethical committees' point of view has been broached up to now. I have the impression that we are trying to assess the investigation only once the project has already been written (the situation of the ethical committee) or once the research has been completed (when we review the scientific evidence to decide whether or not to use one medication or another). Therefore, I would like to comment on the training of researchers regarding the ethics of the research being carried out at both the scientific and bioethical levels. This is critical because obviously the projects sent to the ethics committees will be

carried out more or less well, depending on this training and sensitivity. It is clear that improved projects have been submitted in recent years. On the other hand, I think compliance of the research project depends on the investigator's own ethical commitment. In this sense, informed consent plays an essential role. Obviously, from a legal standpoint, compliance with the need for informed consent could be rare if the investigator were not committed to obtaining informed consent properly.

There are other ethical aspects that investigators (myself included) encounter, for example, the protection of data and biological samples. Genetic information and material is also particularly important due to the social and medical implications.

As investigators, we are also responsible for how these results are reported in publications. In this regard I would greatly appreciate hearing the impression of those attending on what the normal training for investigators is and what their ethical responsibility is as they perform their work. My impression is that training is somewhat inadequate, as mentioned by Dr. Camps. Training in bioethics is not included in medical school curriculum or in the training process for medical residents or investigators. It basically comes from personal willingness and from learning by trial and error, hence regulated training in bioethics should be provided.

Sergi Erill. I would like to comment on one aspect. I fully agree with what Prof. Benatar said regarding the social impact of biotechnology related to food production. On the other hand, from the scientific standpoint I think it is somewhat dangerous to predict disasters merely because they could take place. When isoniazid was introduced for tuberculosis therapy in the late 1950s, an epidemic of lung tumors was predicted, with a peak forecast for 1982. These projections were based on sound research related to the mutagenic and carcinogenic capacity of isoniazid in animals. However, this epidemic never actually happened.

Victoria Fumadó. I would like to thank Dr. Abel for his comments and Prof. Benatar for his presentation on research in developing countries and to reiterate a little what Dr. Abel said. In developing countries, the standards (if possible) must be much higher than those we set here. In answer to the

question he raised, we can never lower these standards. As rich countries we must enforce these standards and not just say, "Better something than nothing", give these countries our leftovers or the medications or instruments we no longer use. We must look carefully at the context and needs of these countries to find out what research is needed in these countries, working jointly with the health departments of these countries, and above all to work, as he said, on education. Informed consent must really be information, which means making this information understandable to those who have never received any kind of training or schooling.

Carlos Alonso. I am working on research to develop vaccines, in particular for *Leishmania*. I am unaware of whether clinical experiments are redundant or not or whether they are repetitive or not. I do know, however, that about 50% of basic research is estimated to be repetitive (you only have to browse the Internet to see that). By repetitive, I mean that exactly the same thing is being done in many countries, with practically no co-ordination whatsoever. This is a fact. This does not mean that the research should not be done, because something major is likely to result from the work being performed in so many countries. However, this is indeed the current situation.

In terms of the problem of the industries discussed here, perhaps a completely radical change in mentality is called for. We should ask ourselves if industry is really the one that should handle the development for promoting the products researched in clinical developments and then offer them for sale. This question is pertinent and must be raised. We should consider whether or not the risk of basic research -with a social purpose- should be accepted by society and, in this case, the state. I feel this yet unasked question must be addressed, whereas we are always talking about industry. First of all, we must remember that developing a product is more costly than researching the product. I am not part of industry, but if industry were required to carry out the research and development, then place it on the market, it is being required to do something it will probably not accept. I would like to mention a specific example. In our laboratory we have come up with a product for the pathological diagnosis of a parasitosis. The development costs much more than the research and is being handled by industry. Consequently, I do not know this question must be raised but I do feel it is quite relevant and important.

Thirdly, it appears that we are not making any difference here (I was speaking to Dr. Camps and she felt the same way) between the scientific committees and ethics committees and probably I feel no need to do so. If no distinction is made between these two committees, we face some extremely serious difficulties because, in my opinion, little or none of the scientific work I review for the evaluation agency would pass high scientific standards. If we also include the ethical value of the project, practically all would fail to meet the standards and we would be left with only 1% or 0.5% of the projects submitted. This is rather serious. Moreover, I am in full agreement with Prof. Benatar, because I have had the same experience with the Patarroyo issue and the malaria vaccine. If we start to discuss the concept of ethics as well as the fairness issue, very few of the projects submitted would be passed by these committees. Perhaps we should come back to reality, look at our surroundings and then decide. This does not mean we should lower our standards. I do not feel we must lower the standards, but certainly the standards must be applied to the cultural, social and economic contexts and must consider the populations where the trials will be performed. The malaria vaccine (which deserves its own discussion), as Dr. Fumadó is also aware and has told me, is in reality the first vaccine that has worked at the population level. It has not worked in other areas, but has worked in two very carefully conducted trials that were published in the *Lancet*. In contrast, in the third experiment with children, I stated that this clinical trial should not be carried out on children because I felt it would not work and in fact, it has not. Why did it not work? Basically because a peptide-vaccine is unlikely to work on children and no others have been found to date. The trial was carried out because there was considerable pressure from all sides, but I was almost convinced it would not work and this has been the case. What does this mean? There is pressure to say that in fact, this vaccine is worthless. Another question: What about BCG? Does BCG work or not? BCG works 0-80% of the time, depending on the population. This does not mean we should toss the vaccine out the window because the effective rate is 0% in some population groups. We do not have to lower our standards, but do have to apply them to the contexts where the trials will be conducted. If we don't, we could be neglecting truly major points of research. I don't know if she could say anything else with respect to the malaria vaccine. I was the monitor of the malaria vaccine trial and spoke to many people in Tanzania and Gambia, as well as in other areas of Sub-Saharan Africa who told me that, "a vaccine that works 31% of the time and prevents malaria

cases 31% of the time; well, until now we have had absolutely nothing". A vaccine that works 31% of the time is practically not allowed in our societies. But in other societies? Just because our standards dictate a level of 80%, does this mean that such a level should be required for these social contexts?

Margarita Arboix. I have two or three comments. First, I am basically in agreement with Prof. Alonso's remarks. Obviously when we conduct a trial in an underdeveloped country, our standards must be high. However, we must consider that these standards differ considerably from the standards of a country in the developed world. Something toxic is unquestionably toxic both here and there. Nevertheless, I would like to mention the case of hormones. There is a pitched battle currently going on between the United States (which says they are not toxic) and Europe (which says they are). We must be truly objective and cold-blooded in our analysis before considering a study in the industrial world or the third world. Demographic factors, standards and needs -as Prof. Garattini stated this morning- differ and because they differ, the committee -perhaps this would be one of the clearest cases- must adapt to the conditions it will evaluate. In this regard, I feel that nothing can be dealt with in exactly the same way.

One aspect I do not wish to address personally as I do not consider myself capable of doing so nor do I feel we have sufficient data to evaluate it properly, is the problem of genetically modified products. I would like to mention to Prof. Benatar, however, that I feel that the example he has used is not the best one as I would probably agree with the classic example put forward by many social movements, i.e., genetically modified plants resistant to insecticides, and that this can pose a serious problem of environmental toxicity. The subject differs, however, when a genetically modified plant creates higher annual harvests because it has rapid growth and this could enhance the food supply in poor countries. Most trials being conducted nowadays have no subsequent monitoring by the ethics committee, making it difficult to assess whether the process has been handled within the prescribed limits. Therefore, I feel the committee should assess the progress of the study, once the trial has been carried out.

I feel this should indeed be a proposal. I am not saying that the committee should evaluate the results obtained -this is precisely why there are scientists- but they should at least evaluate the process followed to obtain this data. This

would undoubtedly provide us with aspects that require such change in our conduct as a committee, as well as aspects that enable us to evaluate the difference between the project preparation process and the final step to obtain the results. Most certainly we would identify some better characteristics for the subsequent process. This is a completely separate issue. Nowadays, the scientific committees and ethics committees do not carry out any subsequent evaluation of these results unless they show interest in following up the result process. I feel this would be of value.

Xavier Carné. I would like to comment briefly on Dr. Alonso's remarks. I work at the Hospital Clínico, in a group headed by Dr. Pedro Alonso that carried out the trials he mentioned. The explanation of why the response to the Patarroyo peptide-based vaccine varies in different communities is quite advanced and there are several mechanisms that explain it, although I do not wish to comment on this right now. I am not an expert nor did I conduct the research. I would, however, like to make several brief comments on research in underdeveloped countries based on several recent articles. One group -I think it was in Uganda- showed some years ago that a very cost-effective measure such as the treatment of conventional sexually transmitted diseases (gonorrhea, etc.) results in a notable decrease in heterosexual transmission of human immune deficiency virus in African communities. This was published in the *Lancet* several years ago and showed very promising results. Recently another group with the same aim has practically found a completely different result, in other words, that treating conventional sexually transmitted diseases with conventional cost-effective therapies did not reduce the transmission of the disease. This is a phenomenon of which epidemiologists are well aware. In tuberculosis (which is a well-known example), the BCG vaccine is not as effective in populations with a high prevalence as in populations with a low prevalence. In all countries, clinical research must be conducted in terms of efficiency: we must look at the reality of what is being actually applied. This kind of study and these discrepancies are normal, explainable and part of scientific knowledge. They have a very clear explanation. There are different hypotheses but, in any case, the transmission of a disease may depend on the prevalence of another disease. There is probably something of this in this field. By this I mean that the basic rules for development and clinical research in underdeveloped countries are quite similar, epidemiologists are familiar with

them and they form part of the conventional rules. We must carry out this kind of study. Right now we are not doing it, or if so, only a very limited degree.

One statement also made by Dr. Alonso that I found very interesting was that we are constantly saying that a huge part of the scientific publications are useless and simple repetitions and I agree. I explained this once to a friend and he told me, "It's obvious why this is happens. Eighty per cent of the millions of intellectuals produced by the human race over time are alive right now." This is true, 80% of thinkers or intellectuals or people who think or have the capacity to carry out research are living right now. Naturally there is an overload. The media and sources of information have grown exponentially and we should not be surprised that we see a lot of worthless things going on. Evidently there are a lot of us and we are full of flaws.

Manuel de los Reyes. I am a clinical cardiologist and particularly concerned about the aspects of bioethics. I feel we are discussing the issues here from the standpoints of several professions because there are conflicts of interests and problems of fairness. What we are doing here is worthwhile, as we are making a kind of self-criticism of our problems, seeking standards and levels not only for correction but also to achieve excellence. Sometimes, however, we are falsely humble and try to provide the answers to the problems of a third and fourth world that are beyond us, which we tend to de-contextualize to some extent. We are unable to understand them completely because we need to listen to the other party to learn their opinions.

In his concluding remarks, Prof. Benatar invited us to move towards a proposal of rational ethical debate on many of the questions he raised. In my opinion, this rational, reasonable debate must reconsider a number of things in each social and cultural context. There are a number of people from different professions here. I feel that any attempt to offer the most rational, objective response possible to many of the problems posed here would require us to reconsider everything, with new ethics for each profession, and this would be basically micro-ethics.

Moreover, the ethics of the health institutions also require adaptation. There are ethics for professionals such as myself who work in the institutions and there must be ethics for the institutions, if none currently exist. In the health care institutions, this would be mesoethics and this is precisely where

health policy and economics questions come in. In addition, the ethics of organizations and companies must be adapted, i.e., we must look at the interests driving them and their financial approach, whether it is simply pure, harsh utilitarianism from neo-liberalism or some other more social-democrat egalitarian approach, etc. Our change of attitudes has to move towards this reflection in the debate that concerns us, so we can improve the quality of what is being done within the context in which we are involved.

The speakers have presented a situation of globalization, but can we speak of a level of minimum ethical standards that can be acceptable in a world characterized by this globalization? Dr. Camps has mentioned problems of fairness. But what about fair distribution? Where are the principles of solidarity and subsidiarity? Where do they fit here? Most certainly they clash with business interests. I believe that required minimum levels would correct these inequalities. In my opinion, there will always be inequalities and diversity, but there are inequalities that must be corrected or prevented, i.e., those that are unnecessary, preventable, not intentionally sought and unwanted. These are the ones that must be avoided. The problem is whether this level of minimum ethical standards should be provided by international law, social standards, ethical codes, state legislation, treaties on citizens' or users' rights, etc. Perhaps an effort should be made to reconsider these models in each social and cultural context, from the ethics of professionals, the ethics of business organizations and the ethics of institutions.

Ramon Bayés. I remember reading in a WHO publication about a specific example that could perhaps be some kind of practical synthesis of Dr. Arboix, Dr. Camps and Dr. Abel's approaches. Whereas women affected by human immune deficiency virus in the Western world are advised to refrain from breast-feeding their infants, in some African countries the recommendation is the opposite because the risk of infection by an HIV-positive mother in these countries is lower than the risk of dying of hunger if the infant is not breast-fed.

Apart from this comment, as a psychologist I would like to call your attention to a problem that, in my opinion, is just as important as having good medicinal products or vaccines. Regardless of the effectiveness of a drug or the accuracy of a diagnosis, if the drug is not taken, it is of no use. In fact, the figures on therapeutic compliance in patients with tuberculosis, HIV,

hypertension, etc. are not very good. Effective administration programs such as the DOTS established by the WHO for anti-tuberculosis treatment are starting to exist, but there is an enormous amount of work still to be done. At least part of the resistant strains of bacteria and virus are caused by improper use of the medications we already have. Decreased efficacy of many antibiotics and some of the problems arising due to the administration of the new retroviral therapy for HIV are, in my opinion, relevant examples. Nevertheless, the growing recognition of their importance, the resources assigned to research the factors that hinder or help good therapeutic adherence are ridiculous, compared to the enormous sums used to create new drugs. In summary, human drug consumption behavior –much more difficult to research than any virus, as Jonathan Mann reminded us several years ago– creates a risk factor that has not received all the attention it deserves.

Juan Antonio Camacho. I am a pediatrician and a member of the clinical research ethics committee at a maternity and pediatric hospital, which means it has special characteristics that differ completely from everything else being discussed here. Both Prof. Benatar and Dr. Abel have hinted at the subject of vulnerable populations. We are at a different level. In pediatrics, clinical trials are absolutely the opposite. The industry pursues huge population groups whereas we pursue the industry to do some types of things, not clinical trials, but simply to be able to treat pediatric patients with medication available on the market. Why? Well, basically because the pharmaceutical industry does not consider it profitable, for example, to research or decide on the antihypertensive agent dose required for a child.

One slide I saw this morning showed 18 ACEI's on the market in Europe or in Italy. Although I am more involved in pediatric nephrology and as far as I know, there is only one ACEI-type antihypertensive agent for pediatric use and probably only two approved by the FDA. As for lipid-lowering drugs, I believe there are none allowed or approved by the FDA, only some exchange resins. This means that the population of children here, not in the Third World, is left defenseless. I do not know who would be responsible for this and whether or not if would be industry. If not, we should oblige the upper strata of industry to implement a study of medication and market products for pediatric patients. Or perhaps the health or governmental agencies could help ensure that children have access to the same kind of treatment as adults. Children are

currently a group lacking protection. Perhaps I am personally sensitive to the issue but I feel that many of us could also share this feeling.

Mariona Portell. I would like to comment on four issues that have come up during the discussion. First of all, I share many of the concerns that have been expressed regarding the lack of relevance and repetitive nature of many investigations; as methodologists we tend to treat this problem under the name of a type III error, by extension of the type I and type II errors of the theory of statistical decision. Nevertheless, I feel it would be hazardous for us to assimilate repetition with irrelevance, without any nuance. As you are aware, replication is a basic tool for creating scientific knowledge that provides arguments to defend the reliability and validity of the findings. In addition, systematically designed replication implies co-ordination and can prevent many irrelevant studies.

The second comment I would like to make is on the concepts of randomization and comparability. The fact that randomized clinical trials are the best research design has been stressed and I agree with this statement if the "randomized clinical trial" label covers all designs that encompass random assignment, even those that impose some restriction on randomization. In terms of causal inference, the critical aspect is comparability. Randomization is simply a technique used for this purpose. I comment on this particular aspect to point out that the way to specify the randomization technique must vary in order to achieve the comparability objective. We could link this with one of the problems raised by Prof. Garattini: When the sample size is small or medium-sized, achieving the comparability objective becomes easier if randomization restrictions are imposed by eliminating important prognosis variables. The diverse variations in block design make it possible to increase the accuracy of estimates when working with small or medium-sized groups. Another way to reduce the scope of the confidence intervals is the statistical control of risk factors known to possibly confuse the results. In short, what I would like to propose are modest solutions that are unfortunately only partial but are applicable (and required by the committee) to all randomized clinical trials that are likely to continue having serious problems with recruiting.

The third comment I would like to make is related to controlling data quality. Regarding this I was quite interested in Dr. Arboix's comments on

whether the committee should evaluate the process that was followed to obtain the data. One of the stages of empirical research that requires greater attention is data management. The strategies used to increase data integrity and quality must be improved, otherwise the acknowledged scientific and ethical merit of the protocol may not become a reality.

Fourthly and lastly, I would like to go back to Prof. Benatar's reference to relativism in his speech. I feel that an institution that adapts its involvement strategies to the situation in which it must become involved cannot be accused of relativism. If their work has been designed while observing certain minimum ethical standards, the work to contextualize an objective and an action plan is justifiable and necessary. As an investigator interested in risk perception and management, I would like to suggest that "contextualism" is a position that attempts to go beyond the limitations of both realism and extreme relativism. I would like to hear your opinion on this subject.

Joan Roca. I am a pediatrician. I would first like to underscore the comments made by my colleague, Dr. Camacho, when he spoke about a certain lack of fairness in terms of drugs used in pediatrics.

I would also like to mention, along the lines of Prof. Garattini's talk concerning the criteria of ethics, the conditions under which the studies are analyzed and lastly, the various results that, to some extent, create some doubt on whether or not the ethics committees can really guarantee good results. In other words, the results were so confusing or so potentially susceptible to a variety of interpretations or that actually show no clear efficacy of the drugs. To some extent, one could consider that if there were a guilty party apart from the investigator, it might be the ethics committee. But I have my doubts as to whether the ethics committee is actually responsible for the results. To what extent must the ethics committee be responsible for the results? It appears that to some degree there should be some assurance that the same individuals attempting to defend research subjects should have some responsibility for defending the subjects to whom the results of the clinical trial are applied. Nevertheless, I feel that in our specific context this simply moves too far away from the actual capacities and possibilities of an ethics committee and makes some attempt to control the results or the information conveyed by the results.

Manuel Canivell. I would like to make some remarks concerning the discussion, particularly on a subject I feel could be important: when talking about standards, not only research standards or ethical standards, but also the quality standards normally used in the pharmaceutical industry. In the Western world, these standards vary practically from year to year are increasingly more stringent. Actually the standards in place today are, in many ethical, production and other aspects, quite different from what we had five years ago and completely different from those of ten years ago. Comparing the contextual moment of ten years ago, we cannot say that we had substandard care or ethics. We had what was appropriate at that time. Dr. Abel mentioned this idea. In the case of the pharmaceutical industry, due to these standards, i.e., due to the fact that the pharmacopoeia and the health authorities are basically narrowing the quality criteria even more and bringing them closer together, allowing fewer variations, we should question whether this makes sense or whether the fact that these products -which fulfilled European pharmacopoeia standards two, three or ten years ago but are no longer considered acceptable by the European or U.S. pharmacopoeia due to tightening of margins- are not acceptable. These products are being tossed out by the world-wide industry literally by the ton, when they could be used in countries in Africa or the Third World.

Solomon R. Benatar. It is a difficult question to respond to, because I do not know to what extent drugs are being thrown away at the moment and what the reasons are for throwing away drugs. If for example, let us say there was a batch of antibiotics which had reached the expiry date, and two questions arose. Were those antibiotics going to be sold at a cheaper rate to a developing country, or were they going to be given to a poor country? I think there is a difference between selling them at a cheaper rate and giving them away. I would also like to know what the confidence limits are regarding the biological activity of those particular antibiotics. If, for example, on a particular date a particular batch of antibiotics had expired, what would be the biological efficacy of those drugs say for a year after that date? Would they be 10% less effective or 90% less effective or a 100% less effective? Without that knowledge of the biological activity of the particular product, one could not generalize about how such drugs should be used. If the motive for selling them more cheaply was to make extra money from drugs that could not be used in the producing country, and if that was going to be done without any knowledge at

all of what the biological activity was going to be, then I would be totally opposed to the idea of paternalistically selling those drugs like discarded clothes. So I think that we need more empirical information. Whatever the drug happens to be, we should have some understanding of what the risks are that this drug is going to be effective or be dangerous in any particular way. If it were possible to develop an understanding of those issues around such drugs as antibiotics, antihypertensives, antipsychotic drugs or drugs for the treatment of AIDS and acquire a specific information regarding what the biological activity might be and also what particular hazards there might be in association with using those drugs, we may be in a better position to answer the question that has been posed. Without this information I think it would be disrespectful of the dignity of other people to sell or even give those drugs to them. If were to be the recipient of those drugs, these are the questions I would ask: what sort of gift am I receiving or what am I paying a small amount of money for, something that works, or something that does not work, or something that is going to be toxic? I would not want to receive those products without knowing the answers to those questions.

Sergi Erill. You have spoken a few times very recently about the lack of clinical studies concerning the introduction of new drugs in pediatrics. You also spoke earlier about the failure to develop vaccines for acquired immune deficiency syndrome. In both cases you have blamed the pharmaceutical industry for this lack of development. Perhaps this is so. But, have you questioned to what extent society is responsible for this? Is it easy for a pharmaceutical industry to sponsor a clinical trial at a pediatric hospital, exposing itself to the possibility that the next morning some magazine, whether of limited or widespread circulation, will appear with a huge headline that says, "Experiments on Children"? Why has no vaccine been developed for the human immune deficiency virus when it was so easy to develop one for the smallpox virus? Because nowadays, society would not allow a vaccine to be introduced unless it offered some guarantees that, from a certain standpoint, are actually hindrances. I imagine this is hard to accept, but as we face many current problems in medicine and therapeutics, we must consider whether or not society as a whole is partially to blame.

Carlos Alonso. I would like to respond to Dr. Carné's comment. I would be very happy to know why the peptide-based vaccine does not work in certain

populations. I wish it were true! I want to know that it is true. But this poses a problem that I consider much more serious than the previous one. In order to understand the mechanism of a vaccine that acts quite differently in different populations, we must perform certain necessary tests. I wonder if there were some ethical standards that would allow this to be achieved with this sole goal. This knowledge would probably give us many clues on how to create a vaccine. I believe that practically no ethics committee would allow us to find out why a vaccine product has not worked in a certain population.

This brings us to another problem: that of the invalidity of experimental research models in most cases (as we now know). In other words, there are vaccines that work very well, for example, for *Leishmania* in some animals, yet fail to function when used in higher species such as dogs. Of course, they also fail in humans. We now know much more than we did before in this regard. People used to think that animal research could be used almost directly to carry out human research afterwards. This posed another problem, the one mentioned at the start by Dr. García Alonso. How can we assess the benefits versus risks? If we look at the benefits obtained from animal experiments, we can assume that there will be benefits. But it is actually extremely difficult, particularly regarding drugs or vaccines, to extrapolate what could happen in a Balb/C rat to what could happen in dogs or humans. The only solution is to carry out research and this brings us to a very serious ethical problem, in the sense that evaluating the benefits is really very difficult when the jump from animal experimentation to humans is so complicated.

This is related to a currently very important problem, that of gene therapy. I shall mention a case in which this problem is truly hard to solve, namely, gene therapy for tumors -gliomas- works practically one hundred per cent with suicide genes in the case of laboratory animals. This was later applied to humans and the results were zero per cent. Extrapolating to humans what had been discovered in animals was the first mistake. The second mistake was simply allowing this research to be conducted on patients with metastasis, specifically with many metastases. I took part in the first investigation by Rosenberg with respect to melanomas. Evidently the effect on a primary localized tumor cannot be extrapolated to patients who already have metastasis. But what ethics committee will allow gene therapy with suicide genes to be carried out on patients with only small primary tumors? None. So what do people conclude? That gene therapy is useless.

We are discussing very real problems that must be evaluated. This does not it mean we should lower our standards, but that society should probably assume both the risks and the burden of damage that may follow experimentation, as mentioned earlier. I don't know if we are aware as a society that the progression of knowledge results in a great deal of anguish. We must reduce this anguish but it will probably be impossible to do so if we really want things to progress. Evidently we must make sure that these burdens are minimized.

Victoria Fumadó. I would like to add to Prof. Benatar's comments in response to Dr. Canivell that, in addition to learning about the biological activity of remnants of medicinal products and medical material from the industrialized world for the Third world, we must also consider the needs of developing countries. We are very often tempted to send remnants of a medicinal product that is not really needed in that country, with the country suffering from some other actual need. There is also a tendency to say that, as a leftover, it can be helpful. But it is not what that country needs. In terms of co-operation, involvement or research in developing countries, we must be much stricter from the position we enjoy as a rich country.

Fernando García Alonso. Based on the most recent comments, I am beginning to feel more enthusiastic about the direction of our discussion. We started by saying that 80% of all clinical trials being conducted are useless. Now we have reached another position where we are claiming more clinical trials on children, more clinical trials on gene therapy, more clinical trials in the Third World.

We have gone from one extreme to another. By bringing both positions together, it appears we have a problem of quality, not quantity. We are actually claiming more and better clinical trials. I feel that Prof. Garattini will agree with me. If 80% of useless studies (probably not actually 80%; we could say 80 just as easily as 40 or 50, so let's say half) are not carried out and are replaced by clinical trials in pediatrics, gene therapy, etc., we would have an interesting overall situation. In my opinion, we should remember that, generally speaking, fewer clinical trials are being carried out than are desirable. My point is that the number of clinical trials being conducted is less than the desirable amount, although I propose that both the quantity and quality be increased by eliminating the "useless" trials and including some that are "useful".

Why is this so important? Why is it so important that we conduct a great deal of clinical trials? Why are there limitations if we not do what we should? This has been said on two occasions and I would like to reinforce it, because it is very important. We are too concerned about ethical problems in clinical research while neglecting ethical problems when providing medical care, in other words, the uncertainty in medical care poses much more important ethical problems than the "few patients" involved in the clinical trials. My point is that we must endeavor to achieve more clinical trials. As Dr. Diaz Villoslada has suggested, I understand that the Health Research Fund is currently implementing a program to finance clinical trials with public funds. This is very important because, by conducting more and better clinical trials through the financing of clinical trials with public funds, we can meet the need for clinical trials in which the pharmaceutical industry is naturally not interested. Perhaps we could oblige clinical trials to be carried out in children or gene therapy or other situations where they would be useful. I would simply like to say that I felt more at ease when the discussion headed in this direction of doing more clinical trials because the current uncertainty of health care probably results in serious ethical problems that are often not mentioned.

Victoria Camps. Before commenting on Dr. Alonso's remarks, I would first like to say something regarding science and ethics, because perhaps we do not all understand the same thing by these two terms. One of the things that I feel has been said about ethics committees is that scientific professionalism is a basic ethical principle. I feel we can not argue this point. We should first evaluate whether things are well done and then start looking at whether they fulfil the principles related to autonomy, fairness, beneficial value, etc.

On the other hand, I feel we are continually discussing two major issues. Moreover, they converge: what clinical trials we are doing and what clinical trials we must do, as Dr. García Alonso has just discussed. It appears that we are continually appealing to authorities that are above the various organizations and partialities, so that they can determine what is most important. This is quite complicated and, as stated earlier by Dr. Abel, is related to the macro problems and to the world as a whole. Perhaps this is the most positive aspect of globalization. We should not lose sight of the fact that there is a kind of globalization that is positive, that consists of asking questions, such as Dr. De los Reyes has: What are the minimum common standards? When we have to

prioritize and determine which trials are the best, we must increasingly reach a higher, broader, more open level. There is no other solution, although it sounds utopian. We cannot discard it.

The other major question that has come up and that affects our subject today is what are the scientific and ethical standards we aim for and whether it is legitimate to relativize them. I was glad to hear the word "contextualize", because if we speak of higher or lower standards we are making the terms absolute, and absolutes do not exist. We have no problem with accepting that there are minimum ethical standards that are universal. But they have one problem: they are too abstract. Therefore, since they are too abstract, they must be applied by relativizing. Relativizing involves running risks. Prof. Benatar said that more empirical evidence is required to determine what risks we are running if, for example, we use a medicinal product that has already expired and therefore is no longer quite so effective. Obviously we need information, we need a more empirical basis, but perhaps the question we must ask is whether it we should run risks. Dr. Bayés said that depending on the country, breast-feeding is better than not breast-feeding, thereby running the risk of being infected with AIDS. Is this a legitimate question? From the standpoint of ethical absolutism, I think the answer is no. No risk is acceptable. But since we are imperfect and the world is the way it is and we can only patch the world up and not redeem it, I believe this question should be feasible.

Silvio Garattini. There is a very large number of things that have been discussed and the temptation is to try to answer to everything that has been said. I will try to say a few things. First of all, regarding the answer of Professor Benatar about the provocative question (if we have expired antibiotics, why do not we give them to developing countries) I would like to be a little cynic by answering that if would really know that these drugs will be able to be effective for another two years, they would not go to the developing countries, unfortunately. They would re-set the expiration date. This is what would happen. So, I think that your answer was a proper one.

In general, I agree with Professor Camps, in that we have always to consider the relative risk versus the benefit. But this is what we do every day in medicine. Most of the drugs that we are utilizing to take care of tumors are cancerogenic, but we run the risk to have a cancer after ten years, because we hope that the

patient will reach ten years. I think that relativity of what we are doing is present in all the medical activities that we are performing.

I want to discuss the problem of my provocative statement that 80% of the clinical trials are useless. There is no contradiction between the fact that they are useless and the fact that we need better clinical trials or that there are large areas in which there is no research. Actually, this may be one of the reasons that we do not have trials of better quality, because we are doing a lot of trials of very bad quality. There is no contradiction at all, on the contrary.

About blaming the industry. I think that we are not blaming the industry. That is the point that must be understood. My point is that we must obviously blame the industry, as everybody else, when they are not doing the right things, or they are trying to set up trials in such a way that they show advantages for their drugs that are not real advantages. But this is a general attitude that we must have against everybody when these things happen. We are not blaming the industry. Actually, I am blaming the fact that we delegate only in industry for research with drugs. That is the blaming, which goes not to the industry but to the scientific community, to politicians, to the government, to Europe. It is not blaming the industry. I would like that it is well understood what it means this complete delegation of studies to the industry. . Some of the aspects have been already alluded to by some of the previous speakers, but let me just make a very small list, which is long, of what we need in terms of public health versus what we get in terms of research from the industry:

– Children. It was discussed. Nobody is doing research with controlled trials in children, and drugs are given to the children without knowing if they are to be effective. There is a very strong statement of the British Pediatric Association, saying that it should not be allowed to give a drug to a child if there is not a controlled trial that has been set up. I think that this is an example. Why don't we do studies in children? Because it is not economical. It costs too much versus the type of prescription that they can get. Is anti-economical.
– We can mention the tropical diseases. Who is working in tropical diseases? They are the most numerous in patients that exist. But what kind of research is going on in terms of developing new drugs. Almost nothing, with respect to the amount of problem that is represented by tropical diseases. We have millions and millions of people that are

suffering these diseases and nothing is done to produce drugs, and yet we are spending a lot of money to produce another antihypertensive agent when we have already 60 or 70 available on the market. That is a consequence of delegating everything to the industry.

– Take the rare diseases. We have 5,000 rare diseases. They represent more than 10% of all the severe pathology that exist in the world. Who is doing research in rare diseases? Nobody, because there is no interest. They will not get back what has been spent in order to develop a drug of this kind. There are too few patients in order to have financial return.

– But there are many other aspects of this kind. All the drugs have a fraction of patients that do not respond to them. If you take depression, for instance, only 30% of the patients respond to the drug. Seventy percent respond to the placebo or do not respond at all. Who is doing studies to find out drugs for patients that are resistant to commonly used drug? Nobody. It is not economical.

– Comparison. Who is really doing studies to compare the drugs that are on the market and have the same indication? Nobody, because, if you do proper comparison, you may find that one drug is much better than the other is, and the other will go out of the market. But from the public health point of view it is extremely important to know which is the best drug in respect to the ones that have less efficacy.

– I mentioned this morning the number of patients that must be treated in certain diseases, chronic diseases, in order to obtain an advantage. You treat 1,000 patients and 900 are treated for nothing because they do not get a benefit; only a few get a benefit. Who is doing research in order to be able to reduce this number? If you find out which are the risk factors, instead to need to treat 1,000 you can treat 100, and that will be an advantage, because only 90 will be treated for nothing. Who is doing that? Nobody. Because there are no resources and because, even if you do the studies, they will not be of benefit to the industry. They will decrease very much their sales and they will decrease the prescription.

– Take another aspect that is, in these days, extremely important. We have now mostly chronic diseases that have to be treated; patients that have a number of risk factors; they are hypercholesterolemic, they are hypertensive, the may be diabetic, they may be nephropathic. We have to

use a number of drugs in order to treat all these risk factors. Who is doing research in order to find out if you need really to treat all the risk factors or if it enough, to obtain the same result, to treat only two out of all these factors? Nobody, because it is more economical, it is more convenient to use many drugs than to use few drugs and to obtain perhaps the same results.

You see how when you delegate everything to the industry, the gap between what is needed by the public, by the patients, and what is given, is increasing, it is not decreasing. This requires what I have tried to say this morning. We need independent funds in order to carry out this research. We will never be able to answer to any of the needs that I have tried to put up, unless we do not have independent funds. How are we going to do it? That is our responsibility. That is a responsibility of the scientific community. It is not the responsibility of somebody who lives on the moon. It is our responsibility to speak up and to convince the governments that we have to do this kind of things. Professor Alonso said rightly that we are doing a lot of redundant research. But why? Because in Europe, we are 15 countries and we have 15 cancer programs which are exactly the same. We repeat 15 times the same thing, and we do not have the courage to say: let us set a common fund and use this common fund in order to improve what we are doing, to do less repetitive work and more innovative work.

I think Professor Alonso has displayed some of these points. We need to have a different attitude when we are talking about clinical trials, when we are repeating things that are always the same, or when we are trying new things. Certainly we risk when we are trying new things, but this is when it is justified to have clinical trials, when we are trying to go beyond the frontiers that have been already established. In that case, we need only to have good ideas, we need only to have good preclinical data, we need to have convincing evidence that what we are doing may have the opportunity to obtain some important results. Sometimes, unfortunately, at the expenses of toxicity. But it must be a calculated risk if we want to improve. I think that the ethical committees should be open to accept risk when there are real important advantages for the public. But they should not accept any risk when there is no benefit at all, because at the end it will be only a repetitive type of work without knowing at the end if something is better or worse than what we have already available.

Another thing I want to say is that, in answer to the problem of the controlled clinical trials, the controlled clinical trial is certainly the best tool that we have available up to now in order to establish efficacy of the drugs. We should not think that all the controlled clinical trials must be with large numbers. There are different kinds of controlled trials. There is, for instance, the end of one technique which is also a randomized clinical trial, but instead to randomize the patients, you randomized the treatments, in a single patient. Good trials can be done in a single patients when there are the conditions (that is chronicity, and so on). You randomize different periods of treatment, for instance with placebo or with the reference drug, with the new drug. This is a very important methodology when the pathology is suitable for this kind of studies.

There is another problem I want to stress. The ethical committee is not only responsible for the approval of a protocol. It is also responsible for following what happens with the protocol. In fact, who is withdrawing sometimes a study when there is evidence that the results are overwhelmingly positive or negative? It is the ethical committee, which means that it is the ethical committee that has to follow. It is the ethical committee that has to make sure that at the end of the study something is coming up in terms of a report. And the hope, more than the reality, is that the ethical committee should require that the negative studies in some way should be published, should be brought to the public attention, because it happens that a very large number of clinical studies that are negative are never published. So nobody knows about these results, and the risk is that there may be repetitions of studies that have been already given negative results. This is certainly completely unethical, but an ethical committee may not know that there are already clinical trials. Therefore, the important to publish also the negative clinical trials.

Joaquín Carballido. My comments are based on my dual position as clinical investigator of urology and from my responsibility as chairman of the clinical research committee of the Hospital Universitario Clínico Puerta de Hierro in Madrid. I would like to share the feeling of progressive enthusiasm evident in the discussion and in Dr. García Alonso's earlier comments. We are moving in extremely diverse fields that, nevertheless, have common points related to the entire scope of clinical research problems. I would like to add one aspect I feel has not been discussed very much and is related to an aspect that is unique to Spain, i.e., the current atmosphere of Spanish health care. This is

key to understanding the progress achieved in the last five years in clinical research, since we cannot analyze this entire issue outside this context. I feel it is essential to clearly emphasize the positive role played by the actions carried out by ethics committees regarding research, particularly since 1994.

I am unaware of whether or not there are any agencies that evaluate health technology. I could not tell you if it could be the Health Research Fund, the Ministry of Health or Insalud. However, we are continuing in our progress and providing answers to very specific issues such as aspects of clinical research (as mentioned) in pediatrics, psychiatry, non-drug research such surgical techniques, heat therapy, cryosurgery, natural history of diseases, etc. One of the important points at this time, and taking advantage of the experience of our speakers, would be to ask if some contribution could be made in order to find the right path towards greater professionalism of clinical research, toward awarding and sanctioning good investigators for their influence on professional field, for their encouragement. We must make it perfectly clear that this activity is not a "hobby" but something truly important and essential that creates risks we wish to confront adequately.

Solomon R. Benatar. I want to make a few concluding remarks if I may. First of all with regard to the context and the relativism of research in developing countries, an issue we have not dwelled on a great deal. I have tabled an editorial that I wrote in response to the editorial in *The New England Journal of Medicine*, an anonymous editorial in *The Lancet*, and also an article in *The New England Journal of Medicine*, criticizing as unethical the HIV transmission studies that were done in Thailand and in South Africa. An analogy was drawn between the Tuskegee Syphilis experiment and the AZT-placebo controlled trials done in Africa. But there are vast differences between the Tuskegee experiment and the very thoughtful HIV transmission studies that were designed in conjunction with bioethicists and ethics committees. What my editorial draws attention to is the need for a little bit more humility, in terms of the application of so-called absolute standards without considering the context. I hope you will read the editorial and the articles it contests and evaluate the balance and the arguments. I have tried to illustrate that it is possible to take morally relevant issues into consideration, and on that basis to construct trials which are equally moral in different context. That is the point I want to make to you about the relativity of studies.

But let me make some other points which relate to the conversation we have been having during the course of today. We can start of with what I think could be very uncontentious statements. The first statement I want to make is that ethical considerations are crucial in all scientific and medical work. Nobody would dispute that. The second point I want to make is that, despite all the work that we have put into scientific investigation over many many decades, we have agreed today that much poor scientific work continues to be done. So, although we claim to be scientific in our intention, although science has made wonderful contributions to medicine, we are agreed that even today there is a lot of bad science going on. So, we are seeking to do better science, to practice evidence-based medicine, and to improve the way in which we conduct our scientific studies, so that the science that we have being doing for many years become even better. These points are not contentious. I want to suggest you that it is only in recent decades that that we have begun to talk of ethics in medicine and ethics in research. We are at an even earlier level in our understanding of what it means to do work in an ethical manner, but we are making progress. This meeting is progress. This meeting might not have taken place five or ten years ago. We have ethics review committees that do not operate so well, but are going to try to make them better. We have not educated people about ethics adequately, but we are beginning to understand that we can do so. With the help of philosophers and others, we are embarking in a program of trying to improve ethics in medicine. So, we should be striving for more and more ethically based medicine, than in the past, no matter how good we think we have been up till now. We can do better. I am sure that we all agree on those issues.

Now I want to suggest something different to you. I want to suggest something contentious, and this has been the thrust of my presentation this morning. However well we think we have done, whatever progress we think we have made, I think our world is in a precarious position. Progress into the future will depend on not only continuing to do what we do well, and finding new ways of doing things, but also on developing a paradigm in thinking about what we are doing. We are going to need to understand that a lot of what is done in medicine and in science is unsustainable. The resources that are being consumed, the extent to which the practice of medicine is being modified, the extent to which some issues are being overinvestigated and others underinvestigated, calls for a switch in mindset, in order to restore the balance.

This is the biggest challenge, because to make this mindset shift is almost like trying to change our religious believes. It requires extraordinary insights to understand that prioritization, rationing, resource allocation on a rational basis are issues we have not adequately addressed. The challenge for the future is for us to address these vigorously.

Finally, let me say that I am leaving two documents for you, which I think that will be a value to you. The first one, referred to in my presentation is entitled "On being a scientist". It describes some of the issues that need to enter the education of scientific people to help them become better scientists. The other is a document developed by teachers in ethics in London, trying to define a co-curriculum of what it is we should be trying to teach medical students in medical schools today, so that they may be more ethical doctors in the future. Again, I think we are at the very beginning of a long pathway towards progress into the future. However I am not pessimistic, I am optimistic. I think we are making some progress, and the debate like the one we have had today raises more questions than it provides answers. But that is good, it means we are thinking, we are talking, we are discussing complex issues, and we are not pretending that in the course of one day we are going to find solutions to all of these difficult problems. But the fact that we are debating them, the fact that we are willing to address them is testimony to the progress. Thank-you.

Francisco De Abajo. I would simply like to make two comments on several questions that have come up earlier. In the end, we agree that research must be carried out, and we agree about when there should be less and when there should be more. We are sometimes restricted by our own words, however, and say things that cause conflict when we stop to think. For example, it has been said that we are allowing the pharmaceutical industry to take the initiative. However, does anyone have a monopoly on research in such a manner that we must delegate it? Don't we have private initiative? Shouldn't we allow things to take place spontaneously? Isn't this one of the values of modern society? Of course. We cannot build barriers in this regard. For example, we are delegating the clinical trial, which is the best method we have, as if we had invented it ourselves and we assign it to the pharmaceutical industry. This should not be so. The methods are there and the initiative is there. We must endeavor to encourage public initiative in topics that clearly pertain to public health. In the end I believe we are in agreement, if we use the words properly.

Secondly, in terms of minimum ethical standards it is obvious we must set some minimum ethical standards that make some attempt at being universal. This does not mean that there can be no exceptions. But the minimum standards must be a basic universal principal, whether investigation is carried out in the industrialized world or the Third World. There are universal criteria that, although abstract, must be applied to research. I feel there is considerable consensus in that there are at least two principles: first, that the risk versus benefit relationship for the subjects must not be unfavorable (I am not saying that research cannot be carried out if the risk is greater than the benefit for the subject, but this should be the exception). In principle, at least the risk versus benefit relationship must not be unfavorable. Secondly, and this is perfectly applicable to investigation, that the balance between the burden and benefits be even.

What about the question of when risks must be run to carry out research?. We run risks every day in everything we do! When should we run risks? According to these two criteria, first, when there is some prospect that the benefit is proportional to the risk and secondly, when the benefit obtained from this research is applied to the group accepting the risk. Therefore, if the research is done in the Third World, it should be used specifically for the group that is running the risk. These are the two criteria in my opinion. Naturally the details must be worked on.

Carlos Alonso. When I read the two articles by Prof. Garattini and Prof. Benatar, I thought they were irreconcilable from any point of view. But I have been attentive to the discussion and after listening to them, I see they are not irreconcilable. I would like to say something that could be conclusive in this work. Industry will not resolve the problems of rare diseases. However, I don't know whether it is needed or if industry should be asked to resolve these problems. In my opinion, we are just trying to pass the buck. As a society, we must solve these problems and we do not want to change our mentality. We want others to resolve the problems. This could perhaps be the main conclusion from this meeting. This conclusion will not resolve the problems but will do something really needed: achieve a radical change in mentality in that there must be solidarity in research projects, which must be resolved by the states. The states are those that have an overall view of the biomedical situation and, consequently, must redirect the research at the global level,

taking into account all these things not considered by industry. Regardless of how much we say that industry is not good, these statements will not resolve these problems. We must redirect the problems. Moreover, we must be careful that this reorientation does not simply consist of creating research lobbies. The industries are not the ones directing anything at present, but the research groups. There is a danger that these groups are the ones redirecting the research in this process. Society must be the one that accepts, in the democratic sense, these challenges and tries to solve them. Society is the one that must redirect research at a global level.

Margarita Arboix. I would like to add something that will perhaps provoke everybody somewhat. I fully agree with the role that must be played by the institutions and governments mentioned here and with the need to define some minimum standards. I would like to give you an example, so you can see how these minimum standards change absolutely, depending on who is managing them. Right now, another hormone is available on the street and also appearing recently in the press because there was a major arrest recently in Spain. This hormone is known as BST, or bovine or porcine somatotropin. When given to dairy cows, bovine somatotropin can increase milk production up to 30-40%. Moreover, the milk is of high quality, with a significant increase in the protein level. In the studies that have been carried out (this was submitted to the European veterinarian committee exactly one and a half months ago), no evidence has been found to date that this milk is toxic in any way for human consumption. However, did you know that this hormone is not yet authorized (it is not in group 4, i.e., nor prohibited nor authorized)? This is due to two main reasons. I believe one is more important than the other is, but this is rather subjective. One, and this is textual and has been written this way, is basically that dairy cows treated with somatotropin have been shown to suffer mastitis, a mastitis that is fundamentally inflammatory but sometimes complicated by infection. Hence, authorization has been withheld basically for reasons related to the animal's welfare. Scandinavian countries, specifically Denmark and Sweden, are those who have raised more objections to authorization of the hormone in this aspect. There is another reason: the dairy quotas affecting Europe, not the countries without milk. Therefore, the governments are the ones that decide, not the industry. This is why I mentioned that I would be adding another idea that could provoke some people.

Fernando de Andrés. I do not want to get lost in semantics. We are all faced with the same situation, along with industry. We all have to survive as a community. As someone just mentioned, some of the problems will clearly not be solved by industry because that's not why it exists. This is not its mission and it does not have the motivation needed to solve them. Nevertheless, someone must solve these problems because they are crucial. If they are not resolved, the community is responsible. This is easy to say and sounds very philosophical, but someone must understand that we are referring to them and take appropriate measures. I suppose there are different ways to take measures. One is for the community to take the initiative. On many occasions, they must do so although they frequently neglect this duty. On other occasions industry should be encouraged to do the kind of research which the community is interested in. Sometimes it tries, although this is less frequent. Since we are being optimistic, however, we should stress this as well, e.g., for orphan drugs. Administrative measures are taken so that drugs that do not bring sufficient financial profits, or for which sufficient financial profits are not forecast, have a less costly development process or so that the patent lasts longer or they receive advice from the regulatory standpoint on how to develop them, etc. This is a possibility, instead of simply criticizing industry. Another possibility (and with this I would like to support my friend, Dr. Erill) is that one of the ways that the community sometimes prevents useful investigations is by so-called over-regulation, something we also experience. Naturally, we must take all the relevant precautions, but not all the precautions that can be taken. This must also be perfectly clear.

Xavier Carné. I would simply like to recommend that everyone read an article (although many of you have probably already read it) in the first issue of the *Lancet* this year that asks whether or not institutional clinical trials can exist in Europe. Jean Pierre Poiselle, et al., posed this question and the response is not very clear.

Manuel Canivell. I found it curious that the issue of orphan drugs appeared right at the last moment because it is a clear example of an issue where the standards have been lowered, as I mentioned earlier, namely, in certain situations the standards are lowered. On the other hand, there have been considerable comments on the role of the pharmaceutical industry in

clinical trials. The pharmaceutical industry is partly obliged to conduct these clinical trials by law. There are some clinical trials that give us the impression that they have no added value. They are simply carried out to comply with legislation. I have nothing more to add. Thank you for your participation. We look forward to seeing you on another occasion.

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