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Ethical Considerations Regarding Access to Experimental Treatment and Experimentation on Human Subjects

Rapporteurs: by Harold Edgar* and Ricardo Cruz-Coke**

* Director of the Julius Silver Program in Law, Science and Technology, Columbia University, New York.

** Director of the Genetic Unit, J.J. Aguirre Hospital, University of Chile.

Introduction

This paper was prepared to facilitate discussions within the International Bioethics Committee (IBC) about the topic 'Access to Experimental Treatment and Protection of Human Rights'. The principal issue is whether and to what extent individuals or groups have a 'right' to experimental treatment, or at least to have access to it without undue government interference. Do such claims call into question the principles and practices that underlie biomedical research with human subjects?

Although the paper draws on shorter papers prepared by members of the IBC, it is not, in any sense, a committee report. There were no preliminary committee meetings, and the annual IBC meeting provided the first occasion for extensive consultation. Superb work on these and similar issues, however, has been done under the auspices of other international organizations, in particular through the joint efforts of the World Health Organization (WHO) and the Council for the International Organizations of Medical Sciences (CIOMS). Their conference reports, and the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Geneva, 1993) for which they are responsible (hereafter referred to as IEG), provide an indispensable road map. Several members of the International Bioethics Committee have participated in the WHO-CIOMS work.

Section I of the paper sets out a brief description and analysis of some issues about access to experimental treatment. Section II reviews a few key international legal texts and ethical documents to ascertain what they say about these problems.

One overall conclusion shared by everyone should be stressed at the beginning. There are interesting problems concerning fair distribution of experimental treatments (although no unanimity exists about whether persons' interests in participating should be thought of as a right). As a practical matter, however, distribution of experimental treatment is a problem of much lesser importance than fair distribution of established treatments. This paper does not address the problem but that it is a much more important issue for political action is clear.

I. Access to Experimental Treatment: Why Is It Important, and What Does It Mean

Access issues became dramatized because of the AIDS epidemic, although one can find discussion of similar issues in prior literature, including such favorites as G. B. Shaw's *Doctor's Dilemma*. But AIDS focused new attention on the need for scientific and medical innovation, and the necessity of taking risks to get it. With AIDS came a gradual cultural transformation in the image of participating in research. When research principles crystallized into international legal and ethical norms, in the 1960's and 70's, the dominant intellectual paradigm - whatever the attitudes of real patients with real diseases - stressed the risks inherent in medical research, and the need to protect research subjects from them. The need for protection was particularly great if the subjects were members of groups that historically were disadvantaged. The AIDS epidemic taught a different lesson: persons facing near certain death from a deadly disease may welcome risk-taking in the name of possible therapy (Edgar and Rothman, 1990). For the afflicted, institutional arrangements may be unacceptable if the result is to slow the pace of therapeutic development, and require the rigorous testing of promising new treatments before permitting their use, despite the fact that there are no plausible alternative cures. Similarly, to protect a prisoner from participation in a therapeutic AIDS experiment may add the certainty of death to the disabilities that result from a criminal conviction (IEG 7 and Commentary).

Yet, AIDS does not remotely constitute the entirety of the access problem. First, there are a considerable number of diseases, like AIDS (or at least like AIDS before the new combination therapies), where physicians' cupboards are essentially empty. Second, access is not one issue, but several issues marching under the same loose banner.

Consider these five different claims, or possible arguments, each of which raises a potential problem of access to experimental treatment. They are at the center of the IBC's discussions. Do any of them have merit? If so, does recognition of their legitimacy require rethinking current research rules?

1. There is the claim that a competent adult should be permitted to choose an experimental treatment if a licensed physician will provide it, without having their joint judgment second-guessed by a review committee or regulators. Government and ethics committees should not interfere with an informed patient's access to experimental treatment.

2. There is the claim that it is unethical to require people who want experimental treatments to accept randomization, with the risk they will receive either a placebo or conventional treatment, as the price they must pay if they seek access to the promising new one. Government should not condition access to experimental treatment on an individual's consent, which is essentially involuntary, to serve as a guinea pig.

3. There is the claim that ethical rules that provide special protection for certain individuals who lack legal competence to consent have the perverse effect of causing impermissible discrimination against vulnerable people. Governments and researchers should not discriminate against the vulnerable in providing access to experimental treatments.

4. There is the claim that government discriminates against classes of people unless it assures that women and racial minorities are frequent participants in medical research. Otherwise, medical products and services will be marketed, and no one will ever investigate whether the product actually works with women or minority patients. One of the certain consequences of the human genome revolution is heightened awareness of the differences among people, and the influences those differences have on illness and its cure. If much disease-susceptibility may be linked to multifactorial genetic analysis, it is likely that cures too will work better on some groups of patients than others for these same genetic reasons. Government denies equal access to effective treatment if it ignores whether products have been appropriately tested for use in significant segments of the population.

This is a somewhat different claim than that the research rules by protecting specific individuals deny them their access to a chance that turns out, more often than not, to have been beneficial. The claim is instead that classes of people defined by sex, race, etc. have, or may have, biologically different responses to therapy. No individual woman may know about or affirmatively seek access; but unless government insists on women's inclusion as research subjects, the data on which product registrations are based will not take account of the products' likely use by more than half the population. Discussion with IBC members suggests that, as a factual matter, this is more of an issue in some countries than others.

5. There is the claim that rules that require individual informed consent prior to initiation of experimental therapy may, in some settings, make it impossible to do research at all, leaving the persons thus afflicted, as a group, much worse off than if research were allowed to proceed. The application of research principles in a manner that makes it impossible to improve the treatments of certain conditions denies those who suffer those conditions access to effective treatment.

Each of these claims has variations and nuances, turning on such issues as whether imminent death is the patient's prognosis; the adequacy of alternative treatments and the like. No doubt there are other access issues, but these will suffice for discussion in a short paper.

Some of these claims raise issues of justice in distribution of a resource, and require the analytic step of characterizing experimental treatments as a good like other goods. Whether one can reject claims of a right to access, by saying 'we have no reason to believe you would benefit from this experiment', is an obvious and key issue. Other claims involve issues of respect for competent individuals' rights to make their own decisions. On what basis may society rightly interfere with their judgment that they want an experimental procedure performed? Still, other issues involve the principle of beneficence. Should we not reject rules that make it impossible to improve the treatments for certain diseases? As is well known, these three principles - respect, justice and beneficence - can conflict in various settings. There is no agreed upon way to assign them weights.

A. *Some Consideration of Justice and Participation in Experimental Protocols*

Our analysis starts with claim three. But we want to repeat the cautionary note on which this paper began. The principal ‘access’ to medicine problem, worldwide, is the inability of so many people, in both rich countries and poor countries, to secure medicines and treatments that are known to work well, and that are available to the rich at a moment’s notice. The new AIDS drugs will provide another instance of this familiar problem.

The failure to provide a reasonable level of health care to all persons that need it is principally blamed on the costs involved, but also on medical infrastructure and the absence of services in many areas, and sometimes to patients’ ignorance. It is a tragedy nonetheless when someone dies for want of medical attention that could easily save him or her.

Whether this failure violates international human rights obligations is a topic with its own huge literature. A large number of international and regional documents solidly ground a right to basic health care and the principle of access to health care without discrimination. This paper cannot present that material and stay within reasonable length. Our failure to discuss it in no way diminishes its central importance.

The problem of securing adequate health care to everyone is so vast, and the international community’s attention to it is so patently inadequate, that worrying about whether experimental treatments are fairly distributed may seem precious. Yet, many claims to a right of access to experimental treatment are simply derivatives of these arguments for general access: if experimental treatments are, more likely than not, an improvement over the care administered routinely, then principles of justice may require that there be no artificial barriers to attaining them (IEG 10 and commentary).

Present practice is justified, however, on the rationale that temporary limits may be necessary to establish that an intervention works, and that high priced interventions become cheaper over time. Novel treatments (bone transplantation provides a good example) tend to be very expensive when they are introduced and access to them is initially extremely limited. As bone marrow transplantation became an established procedure and more centers became involved, it has become cheaper and access has become wider. This remains the pattern with currently experimental therapies (cell therapy, gene therapy and therapy with expensive biopharmaceuticals). Their introduction on a highly restricted basis and at high cost is justified by the expectation that if they become established successfully access will rise and cost will fall.

Claim three focuses on the problems vulnerable people face as a result of the presumption against their participation in research. It has a somewhat different thrust. One goal of bioethics has been to limit involvement in research of those who cannot consent for themselves. These limitations were adopted because history teaches their wisdom: the worst abuses in the history of research medicine have always been committed against the vulnerable. Have we nonetheless gone too far in burdening their participation in therapeutic clinical research?

If the opportunity to participate in some medical research is properly viewed as a benefit before its results are known, a proposition that is controversial and that some members of the IBC would reject, then it seems harsh to deny that benefit categorically to vulnerable people such as children or the mentally ill. That is the result if they are deemed incapable of consenting to any experiment, even if the benefits seem greatly to outweigh the risks.

Most competent persons’ access to experimental treatment turns on a number of variables: their physicians, where they live, their initiative, and simple chance. In the United States of America, with AIDS and increasingly with other diseases, there are efforts to publicize clinical trials, so that, for example, ill people can ascertain what clinical studies are available by use of the Internet. Legislation proposing a registry has been introduced in Congress. If that trend continues, a real sense of entitlement to participate, or at least to a place on a queue, may develop. At present, who gets what is largely the result of chance within the groups of people that researchers look to as potential subjects. If researchers affirmatively exclude groups of people such as children or the mentally ill (or women of childbearing age), there is a real discrimination issue. Exclusion is not by happenstance.

At present, persons incompetent to consent are blocked from clinical research by rules that tell their guardians their wards cannot participate if the research involved can be done with someone who is competent to consent. Moreover, all research with persons incapable of consent must struggle with concepts like ‘minimal risk’, etc..

The discrimination claim presented by such person, or those representing them, implicates both justice and beneficence principles. Why should a person ill with AIDS-related mental illness be excluded from testing a drug that may save his vision? If other ‘normal’ volunteers think that the trial, on balance, is a good idea, why cannot parents volunteer on behalf of their son? One’s attitude about whether this problem is important will be much influenced by whether or not one believes that expectations of benefit from research participation are realistic. Yet the present rules seem to assume that the risks of clinical research more commonly outweigh the therapeutic rewards.

The IEG urges the minimally acceptable principle, namely that if experimental but promising therapies are permitted widespread use, through programs such as so-called treatment INDs or ‘parallel track’ release of drugs, then the mentally ill should have access to them too. But the Commentary argues against including the vulnerable in ‘formal clinical trials’. It defends neither that exclusion or the related proposition that vulnerable people should only participate in research that is linked to the cause of their incompetence. It would seem, however, that participation by competent people in the same trial would prove some assurance that the vulnerable were not being exploited.

The beneficence issue is whether the protections we accord the incompetent make it impossible to do research on their problems. Obviously, this will be more true of some groups of incompetent persons than others. With the increasing numbers of elderly people, there will be more persons with various forms of dementia. Yet, Alzheimer’s disease is such a large problem (and lucrative market) that no one is likely to turn from it. By contrast, children may become therapeutic orphans with respect to diseases where adult therapies exist, and disease onset during infancy is rare. Developing therapies for children, and indeed testing whether adult therapies work in children, is not seen to be worth the expense and inconvenience. The additional problems of securing consent, and doing research that creates no more than minimal risk during the purely investigative phase, may tip the balance against the effort.

B. *Respect for Persons*

Claims one and two assert that respect for persons requires us to let competent well-informed adults make up their own minds about experimental therapies. We do not do that today. Our present practice reflects the judgment that government needs to balance the ‘right’ to access to experimental treatment without the necessity to agree to take part in a trial against the public’s ‘right’ to be protected against the risk of harm from inadequately evaluated drugs. The thalidomide tragedy still casts a long shadow.

Consider this hypothetical situation as one vehicle for considering issues raised by the balance we now draw. An individual is suffering a disease or condition that will likely kill him in the immediate or reasonably near term future. He desperately wants (or consents when asked by the physician) to undergo an innovative medical therapy that a physician or team of physicians is prepared to try as part of a research project. In the opinion of appropriately informed third parties, perhaps an institutional review committee or a state regulatory agency, the procedure has no realistic chance of success. Moreover, it has not been adequately tested or readied for clinical introduction. The researcher’s request to proceed is denied; the patient is denied access to experimental therapy; the patient dies.

Does this happen often?

Curiously, public attention is more frequently drawn to this situation when the procedure gets done, despite professional sentiment that the procedure is ill-advised, than when it is stopped. Such a situation may be illustrated, perhaps, by the controversy over the first uses of the artificial heart, or the transplant of a primate heart to a baby. Enormous publicity tells the story of the ‘heroic’ effort; the procedure fails; and then, critics ask why did the institution-based review committees (IRB) let them do it.

Yet, researchers who want to proceed are told ‘no’ - or more commonly ‘not yet’ - frequently and patients die. The situation gets little or no publicity because most of the time the patients who are denied access never know the chance they lost. They are not approached to consent to the procedure until after the independent review committee approves the research protocol. Indeed, the most frequent ‘denials’ result from decisions by the researchers themselves that it is pointless to ask for approval because, for example, the product has not completed animal studies or cannot yet be manufactured consistent with government regulations setting forth good manufacturing practices. Researchers complete the preliminaries rather than filing poor applications.

When individual patients do not know they have been denied access, they obviously cannot argue their right to choose, based upon principles of autonomy. Only rarely is a patient so well informed that his individual voice influences the process, as apparently happened when approval was granted to try a baboon to human bone marrow transplantation for HIV. Yet, clearly lots of patients are denied clinical research opportunities they would accept in a moment because of the investigators’ desire to follow required research practices. It is hard to reject the patient’s autonomy interests, even if understood as self-determination within reasonable contextual limits, simply on the grounds that our rules and practices have been arranged so that they never learn that they had such interests.

The claim that we might make on behalf of these people, however, strikes at the heart of the whole system of protection from research risk. The institutional and regulatory review processes the international research community has created, in the name of research ethics, are intended to deny patients access to some experimental treatments, i.e. those that an independent committee believes it imprudent to begin studying in humans, despite the sponsoring physician’s readiness to proceed. It cannot possibly be ‘unethical’ to follow the procedures good ethics requires, or can it?

The case for going forward might be framed this way. No one doubts that death for the patient is the result if nothing is done. A licensed professional believes that the experimental approach offers some slim hope. What stake does the community - represented by a well-informed review committee - have in the matter? Assume that the committee is right in nearly all cases, and that the procedure will nearly always fail. What harm is done by trying the procedure out? Every once in a while the committee might be wrong. After all, the ethics committee members rarely know as much as the principal investigator. (Indeed, in the United States of America, an ethicist, not a scientist, might cast the deciding vote.) And, for sure, the research will produce information.

Is there, at least in liberal democracies, a basis for claiming that the State should not intervene if a person certain to die soon from a disease no one knows how to cure wants experimental treatment performed that a licensed physician thinks should be done as part of a research project? In the United States of America, two important federal courts have recently issued opinions holding that the State may not constitutionally prohibit licensed medical professionals from helping a competent patient who is terminally ill and in great pain to kill himself! (The United States Supreme Court is now reviewing this.) Is there no constitutional issue when the State stops a different physician from attempting to cure the very same patient with an experimental drug or procedure, simply on the grounds that drug did not secure committee approval or FDA clearance?

One argument that supports the present procedures is that there are many fates worse than death. If a procedure extends life by two months, but those months are spent incapacitated by stroke, the patient has gained little. Similarly, if the patient spends weeks in arduous cancer therapy that fails, the pain and suffering the intervention caused must be judged a harm. Underlying our current practices is the belief that the patient *in extremis* cannot always judge whether the burden and inconvenience of participation in novel research is justified. Many people will take any risk (and pay any monetary price, triggering concerns about fraud) if told that the alternative is death. Their incapacity to see and accept their situation is precisely what occasions the need for protecting them.

(If this argument is credited, however, it has implications for whether terminally ill patients are properly included in research projects. If they cannot fairly weigh for themselves whether to participate in research that a committee will not approve, why are their reasoning faculties any different when the research proposal does seem worth doing, especially if the committee acknowledges the research involves testing compounds that have a low probability of success?)

It is hard to believe, however, that the ‘fate worse than death’ argument actually accounts for our practices in interposing committee review. After all, the committee exercises the same supervisory responsibility when the patient is ill, but not dying. Is it possible to argue that experimental subjects can never evaluate the situation? The situation supposed is one where the physician (or team of them) wants to commence a clinical research protocol but the committee says no. Let us suppose the committee or review body is usually right. Why should its judgment control if the patient - having heard whatever the arguments the committee advances - still disagrees? Standard accounts of adult competency seem to call into question the universal practice of letting the committee (or a regulatory agency such as the Food and Drug Administration, FDA) have the last word.

The defense of contemporary practice that better squares with what contemporary societies actually do is the utilitarian one. The research review system facilitates the orderly creation, testing and widespread use of new therapeutics. The disappointments that eager physicians and patients experience in implementing novel approaches are a price properly paid for the collective good of having public confidence in the research system, and the ability to monitor - and certify - the validity of new therapeutic approaches. These interests are especially legitimate ones because the public finances a substantial portion of both the research and the later use of the products and procedures in question. The person denied access today is the beneficiary of the system’s past success, and cannot insist that society permit unsupervised introduction of therapeutics.

To accept the validity of a claim that people have a right to try whatever medical intervention they want would substantially undercut the entire structure of research ethics. We should not accept it.

Claim two, and the ethical problem represented by random clinical trials (RCT), is a much closer issue. The random clinical trial is ethically controversial (as indicated, in part, by the refusal of some countries’ review committees, e.g. Tunisia and Chile, to approve them). A large literature exists about it.

Unlike the situation where a patient wants to push faster than the collective judgment thinks is appropriate, the experts here agree that the research should be done. The question is whether giving some but not others the new drug or procedure is defensible, particularly if all participants affirmatively prefer to take the new treatment.

Although countless variations are possible, assume that a patient wants a promising new therapy, and the review committee (or regulatory agency) agrees that it is promising and should be tested against a placebo or standard (but not fully satisfactory) therapy. To increase the drama, assume the patient suffers from a condition that will soon kill him, and there is no other therapy. The new therapy may or may not improve the situation, and indeed may make it worse, but without it, the patient will, in all probability, soon be dead.

Is it ethically justified to permit access to the treatment only through a controlled trial where the patient has the substantial chance of getting a placebo? The patients who get the placebo will continue their well-mapped progression down a fatal disease path. Are they not, realistically, conscripts rather than volunteers?

The literature defending random trials within a deontologic framework focuses on the uncertainty that exists about whether the novel procedure works or not. The ethical constraint is that there must exist ‘clinical equipoise’. The researcher does not have any way of knowing whether treatment A is a better choice than treatment B or non-treatment. The new treatment may be unpleasant, and almost surely carries risk, for drugs that can harm no one are not likely to benefit anyone either. Indeed, if the researcher believes strongly that the new treatment is better, then he or she should not participate in the clinical trial. Therefore, the

patient who is randomized is not denied ‘access’ to anything of known value. He is given treatments that are different, but there is no basis to prefer one treatment arm over the other, *ex ante*. The harm done him is equivalent to forcing him to put his money on ‘red’ rather than ‘black’ at the roulette table, rather than letting him express a preference. Such empty preferences are of little social weight given the importance of testing new medicines.

Moreover, the history of medicine is filled with occasions when random trials prove that ‘no treatment’ was much the better choice, despite strongly held professional intuitions to the contrary. Who would have guessed that smokers taking carotene do worse than those who do not thus supplement their food?

Much of the access debate turns on whether this ‘equipose’ defense of the RCT is judged convincing. For example, consider once again the argument that we discriminate against the mentally ill by blocking so pervasively their research participation. What difference does it make whether the mentally ill are excluded from clinical trials? If there is no reason to believe that participation is beneficial, then there is no harm. If the premise is true, the argument for inclusion reduces to the claim that the State should not interfere with choices autonomous guardians make for their incompetent wards. Such an argument seems ludicrous on its face, given the importance of protecting wards from their guardians’ potential breaches of duty.

The premise, however, that no one ‘knows’ anything that is worth relying on, until the proposition is proved by a clinical trial, is at odds with common medical practice.

The proposition that many random trials provide confounding results is true. Curiously, it is almost always established by anecdotes. What percentage of Phase 3 drug trials yield products that are ultimately approved for marketing? The appropriate question is whether, and, if so how often, random clinical trials are used when fully informed clinicians would strongly intuit that a patient is much better off getting a new treatment than remaining untreated, or treated by conventional therapy. In those settings (which are a subset of all RCTs), what percentage of the time are the clinicians wrong? It is hard to believe they are wrong more than half the time. After all, commercial organizations like pharmaceutical companies do not frequently spend millions of dollars running Phase 3 trials if their scientists are genuinely in ‘equipose’ about whether their product works.

It is important to note also that medical practice does not and never can primarily consist of administering procedures or drugs in circumstances where their safety and efficacy has been ‘proved’ by RCTs. First, there is too much biologic variability. Indeed, the strength of claim four - women’s claim to great inclusion in the research process - is that we do not now seek research groups that mimic the population. People organizing clinical trials should make sure the population is fairly represented among research participants. Second, new treatments like drugs are (usually) tested in two groups of patients for a given indication, and then put on the market to be used in whatever ways accumulated medical experiences dictate is wise. Clinical experience may dictate use of the drug at doses higher than, or for conditions other than, the ones the drug’s labeling recommends.

To be sure, the regulatory agencies try to regulate commercial sponsorship of off-label use. A company cannot claim an effect it has not proved to the regulator’s satisfaction. But once marketed, drugs find many uses beyond those that are in any sense proved. Indeed, claim four - women’s, children, and racial minorities ‘access’ issue - is precisely that. No one ‘knows’ - in the ‘proven’ by RCT sense - whether drugs proved efficacious on Caucasian males have the same therapeutic profile when used in populations that are different. Children, for example, are not little adults physiologically. And yet, society has been content to permit clinicians to develop their knowledge about the efficacy of treatments in pediatrics through experience.

Random clinical trials can, of course, be easily justified by utilitarian argument. The collective welfare is served by following procedures that assure that new therapies are appropriately tested before they are put into widespread use. Whatever coercion exists in making patients accept the risk of non-treatment in order to get access is justified by the greater good their quasi-involuntary participation provides. Society cannot even pay for all medical treatments that work; at very least, society should make sure it does not finance those

that do not work - let alone expose thousands of patients to their side effects. Some people in the AIDS community are now taking this view about drug testing. The policy of bringing drugs quickly to commercialization has worked to increase patient access; but it is hard for patients to know which drugs should be taken when. The new drugs are not easy drugs to take, and they can cause serious side effects. It is very difficult to get good research data once all kinds of drugs are in widespread use. Therefore, perhaps they should be better tested before they are released, even if access is denied while testing.

There is, however, some incongruity in defending RCTs by reference to utilitarian values. The entire edifice of research ethics rests on principles that deny society's right to make a person a research subject without his genuine consent. For many people, the random clinical trial is wrong if it cannot be squared with a rights-based approach. If consent is properly called involuntary, then the practice is wrong. For people who hold this view, the analytic step of denying one can have any 'right' to an unproved treatment is key, for then the securing of consent to what is available only by discretion seems uncoerced.

Whether or not one finds the ethics of the double blind random clinical trial problematic (and it is clear that most members of the IBC do not), one has to wonder whether in the future the worldwide explosion in information technologies will limit its use, at least in high visibility settings like AIDS. The Internet permits patients with the same disease to find one another to share their experiences in easily accessed 'chat' groups. If everyone in a clinical trial can talk about what their post-medication symptoms are, and get up to date information about the known side effects of the active arm of the study, is it likely that the placebo group members will not ascertain their status? If they do, will they remain loyal to the trial, or will they enter a different trial? As Herranz Rodriguez (see Volume II of Proceedings) points out, the contemporary ethics rules insist that a patient be told has no duty of loyalty.

It may be, however, that information technology, while making RCTs more difficult, provides an important supplement to them. With the consolidation of medical providers comes a better chance of routinely tracking health outcomes measure. We might seek vastly more information about each prescribed use of a drug, and computerize the results. At some point, we may have to ask whether tracking is consistent with data secrecy concerns.

C. *Beneficence*

We turn to claim 5, which is in some respects the most difficult. People cannot get access to improved treatments if research rules block all feasible means of testing them. If, as a practical matter, particular kinds of research cannot be done at a reasonable price consistent with securing individual consent, and yet most potential subjects would regard doing the research as a sensible policy, and indeed if a vote were possible, would vote to participate in these research projects by a wide majority, why should the research not be done? The question is implicit in Shapiro's and Lachmann's observation that the great advances in public health achieved by the early vaccines might not have been accomplished pursuant to contemporary research rules (see Volume II of Proceedings).

Consider Professor Lachmann's observations, delivered in course of group discussion of the 'access' problem. Both the more rigorous definitions of personal autonomy and an absolute requirement for informed consent may come into conflict with the needs of public health and some balance needs to be achieved. The conflict arises in particularly stark form in relation to infectious disease. Field trials of vaccines are mostly carried out in children too young to give informed consent. The vaccination programs aiming to eradicate an infectious disease entirely (smallpox already achieved; polio in progress and others, particularly malaria, in prospect) require a high level of participation. Although malaria eradication is still in the future, the most promising approach may be 'transmission-blocking' vaccines diverted against the sexual forms of the parasite. These vaccines will not provide a direct benefit in those vaccinated. The effect is on the capacity of their blood to infect mosquitoes that bite them and thereby to protect others from infection. If this approach turns out successful, field trials will need a very huge uptake and the possibility of side effects will have to be accepted.

The recent public policy debate in the United States of America about whether and how to make special rules for research in emergency settings can also serve to illustrate the problem (US Dept. of Health & Human Services, FDA, Federal Register 1995).

Each year, approximately 350,000 people in the United States of America suffer a sudden cardiac arrest. Most die, while many others are irreversibly harmed by complications such as brain damage. In the cases of patients who survive, the risk of recurrence is high and the protection offered by easily implantable cardioverterdefibrillators exemplifies the important successes that can be achieved. One of the most critical challenges is to find ways to improve the initial survival rate of individuals who are typically unresponsive and unable to communicate. Currently, despite efforts to instill basic life support education (i.e. standard CPR techniques), only a small percentage of individuals who suffer sudden out-of-hospital cardiac arrests are resuscitated by bystanders. Few survive to leave the hospital. This percentage may be as low as 1 to 3 percent in some large metropolitan areas, with the best results estimated to be only in the 25 percent range. Given the large number of sudden cardiac arrests annually in the United States of America alone, even small improvements in care offer enormous lifesaving potential.

Standard CPR methodology was largely developed on a mechanistic and theoretical basis. Improvement or rigorous challenge of the methodology is complicated by the difficulty in obtaining approval to undertake studies in out-of-hospital cardiac arrest victims. The inability of most cardiac arrest victims to provide the requisite informed consent has proved a significant barrier to evaluating either treatment options available in other countries, or new techniques devised in the United States of America.

Is it permissible to enroll unconscious patients, who are in life-threatening situations, in random clinical trials of new resuscitation techniques, including techniques that involve highly invasive procedures and carry a risk of causing immediate death? FDA has issued proposed rules (since made final) to permit research (with special IRB requirements), despite the fact that there can be no informed consent by or for the patient. FDA's documents and their reasoning seeks to align the result with conventional research ethics, but it is hard to avoid the conclusion that policy-makers, researchers and, to some extent, the larger community have decided to ignore the usual rules because they get in the way of a good result. It is wrong to block research in an important area. If insisting on informed consent would block it, then informed consent requirements must be rethought.

How far down this path can others rightly go, for the same reason? If, for example, vaccine trials are fully warranted, but necessarily involve exposing third parties to risk, are they not also legitimate? What about research in the developing world, on diseases peculiar to its localities, where the individuals whose cooperation is necessary for research cannot understand the research procedures used, or the risks they entail?

Once one surrenders the notion that consent is an absolute requirement, it is not clear what the next stopping point is. And yet, to ignore problems of personal and public health also imposes serious consequences.

II. Law, Research Ethics and Access

The creation and widespread international acceptance of special ethical rules for the conduct of human biomedical research is, in many ways, the signal accomplishment of the postwar bioethics movement.

On issues such as abortion, euthanasia and artificial reproduction, there is little consensus on first principles, and different societies have taken sharply different positions. On human research principles, however, there exists a widespread consensus: research may be conducted only after review of a protocol by an independent committee, with the informed consent of the participant, and with special protections for those who cannot consent because they are too young, too ill or mentally incompetent.

So far as the authors know, there is no dissent within the relevant international communities, of both researchers and governments, that these principles are in fact the appropriate ones.

Moreover, the international consensus does not rest on one or two international reports or national laws, that an indifferent world has accepted because no one cares much about the underlying problems. The extraordinary thing about bioethics is how much these moral issues matter to people all around the world. The concern has found expression in a flood of international and national reports, both by independent commissions and professional groups, in legislation and in judicial decisions. On the core questions of the legitimacy of scientific and medical research, and the basic criteria for including patients in such research, the world seemingly speaks with one voice. Scientific and medical research is important and must proceed, but it must do so in accord with the fundamental principles of human dignity. The future universal declaration on the human genome and human rights is another powerful expression of this viewpoint.

Observers should be cautious, however, whenever unanimity exists on matters so complex. First, the fact that there is a consensus on principles does not mean that those principles are effectively applied in the actual supervision of research. In many parts of the world, there are not enough people who are trained in the analysis of research protocols, and the ethics of research to discharge fully the responsibilities that the principles of research ethics require. Even in societies that have no shortage of people who can do the work, the question whether institutional committees can effectively review research in the time they are prepared to devote to the problem is a real one. Independent committee review can be a rubber stamp. For example, in the United States of America, a recent government report was pointedly critical of the burdens imposed on IRBs in relationship to the time available for work (United States General Accounting Office, 1996). But to the authors of this paper, at least, the key point is that the very existence of the institutions and procedures of review have served to enhance dramatically the quality of the research that physicians and other researchers propose, and to increase the likelihood that the research will be done in a way that respects the rights of those who participate in it.

A second note of caution concerns the facilitative role that research principles play. They do not simply set limits on what scientists and physicians may do (although, of course, they perform that role). Their role in granting permission for research is just as important. They mark out a path that researchers may follow. If researchers take that path, they are secure that they have their society's consent to investigate. When no such formal rules existed, for example before Second World War, it was much less clear whether intentionally putting people at risk was ever permissible, and what the consequences would be if there were injuries or deaths in the course of a research project. Research was done, of course, but no one knew for certain the professional and legal consequences if bad things happened. When uncertainty exists about whether the activity is truly legitimate, researchers want to do research in places that will not get noticed, i.e. using the most vulnerable persons in their society as research subjects. No one follows closely the fates of the mentally retarded, the homeless, the patient on the ward, and that is why the greatest abuses have always been in research where they were participants.

At present, ethical researchers need not fear the sunlight. The difficult point is that access issues can get lost in the process of securing consensus between communities of researchers and the broader community. There are, sadly, an endless supply of diseases and problems to research. For the research community as a whole, what is important is knowing how to be able to work on problems that are important and interesting. If rules regulating research make some set of problems - say health problems linked to mental illness - much more difficult and expensive to research than, say, heart disease, one solution for researchers is simply to turn disproportionately to heart disease as a problem. The potential losers are people whose diseases get passed over because the diseases cannot be investigated, or cannot be investigated without spending time and trouble on ethics issues that do not in researchers' minds warrant the effort. And, if these neglected persons are the vulnerable and powerless, their perspective may not be adequately represented by the political processes of the broader community. The community wants reassurance that historically familiar yet terrible research abuses will not reoccur. It has done nothing, however, to end the isolation of the vulnerable that largely accounts for the problem in the first place.

Groups like the IBC have an important role to play, then, in tracing through who the winners and losers are in a world that does not permit equal access to experimental therapies, and in raising concerns if those who are disadvantaged by denial of equal access are indeed the most vulnerable members of society.

Third, and finally, to say that there is consensus does not mean that each country handles particular research problems the same way. Brief papers describe the situation in the United States of America (Katz, 1997), Sweden (Fuxe, 1997), and Tunisia (Hamza, 1997) (See Volume II of Proceedings). It is useful to compare their practices with those of Chile.

Tunisia controls clinical research through the Ministry of Health; Chile and Sweden have committees based at local hospitals. The United States of America also uses institution-based review committees (IRB) but, as a matter of federal law, they are strictly necessary only for federally funded projects and with experiments subject to the food and drug laws (i.e. biologics, drugs, medical devices). As a practical matter, however, nearly all United States of America formal medical research is approved by IRBs.

Tunisia and Chile both prohibit financial payments for participation in research. They also prohibit research on dependent persons, and clinical trials with pregnant women as research subjects. The United States of America permits each practice in some circumstances. Moreover, in the United States of America, patients who are terminally ill may be research subjects. In Tunisia and Chile, the practice is forbidden. In the United States of America, the random clinical trial is the preferred method for evaluating the safety and efficacy of new drugs. Such assignment of patients to one or another treatment groups by chance of is done in Sweden too, although the practice is perceived to raise difficult issues. By contrast, in Chile, the ethical committees in the university hospitals frequently will not accept randomization and placebos.

No doubt considering the rules applied in more countries would require a worldwide grid of great complexity to describe issues like the permissible participation in clinical research of mentally ill subjects, children and terminally ill patients. And yet these rules are the ones that determine who cannot get access to experimental treatments, and that is, we believe, a major part of the access question. Is it fair to say there exists a consensus when there is so much variability in detail?

For the authors, the differences seem more ones of detail than spirit. The remarkable thing is that the review process followed, and the institutions that carry out such reviews are so similar, despite vast differences in other aspects of culture and medical tradition.

A. *International Obligations*

The consensus about research ethics and procedures depends upon overlapping legal and professional norms. The historical starting point, in terms of international legal obligations, was the Nuremberg Code of 1947, issued as part of a judicial opinion by an international court convicting Nazi physicians for killing and injuring persons while ostensibly engaged in research. The judges expressed in the Code what they determined were widely agreed upon professional rules and norms about when research that risked physical harm is permissible. But the Code, which did not benefit an individual and responded to the question whether conduct that was otherwise a criminal assault (or homicide) may be justified because its perpetrator did it for research purposes. The answer was no, unless stringent criteria were met (Cruz-Coke, 1994). The Code's application to research settings where the subject may benefit does not follow as a matter of course.

The Nuremberg prosecutions, it cannot be emphasized enough, had nothing to do with the problems of medical research combined with therapy. Moreover, and perhaps for that reason, the Nuremberg Code did not explicitly discuss the circumstances in which therapeutic research with incompetent persons is permitted, if it is permitted at all. Proxy consent is not mentioned.

While the Nuremberg Code did not mention the issues that underlie the access problem, the absolute character of its prohibitory language continues to have an impact. For example, the Code seemingly bars non-therapeutic research creating any serious risk when true consent is impossible. (By contrast, it is arguable that non-therapeutic research that puts such people at 'minimum' risk is permissible under Nuremberg, because the researcher's

conduct is not presumptively criminal, given that the risk of injury is remote.) The Code's apparent position, for it is derived by implication, has widespread support in the literature, and is echoed in many subsequent national and international documents. The IEG, however, is prepared to permit research, on some occasions, if there is 'slightly' more than minimal risk.

The important point is that this position was derived from human rights principles, from the top down, rather than by looking at whether there are important categories of research that are made difficult or impossible to accomplish under such a regime, and weighing who wins or loses by abandoning that research. For example, there are serious doubts whether Phase I drug testing for cancer drugs should ever be permitted with children as subjects. If the purpose of Phase I tests is to determine appropriate doses, and the practice is to start with low doses then raise them, the likelihood that a child who is the first participant will benefit is vanishingly small. Shall we, for that reason, abandon the effort to test and improve new cancer therapies in children? The habit is to label such tests 'therapeutic', but in so doing that concept is stretched to the breaking point (Ackerman, 1995).

Article 7 of the Covenant on Civil and Political Rights, adopted by the United Nations in 1966 and effective as of 1976, is the second major international document to treat experimentation. It states:

No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation.

More than 100 States have accepted this obligation. Its scope is problematic. It may be read to prohibit only those experiments that, by their very nature, are properly deemed torture or cruel, inhuman or degrading treatment. When experiments may be called torture, they are wrong. This narrow reading explains why Article 7 says nothing about proxy consent or research with incompetents.

If it is read this way, Article 7 does not treat States' obligation to regulate clinical research practices, or to concern itself with access to experimental treatment issues more generally. Yet, this limited interpretation of Article 7 is a difficult one to defend. Ordinary legal principles prohibit behavior that is properly called torture or degradation, even if there is consent. The premise of Article 7 is that medical experiments are wrong without consent, but legitimate with it. Thus, an argument might be made that 'subjecting' persons to human experimentation without their 'free and informed' consent is itself degrading (Katz, 1993).

If 'subjection' to medical research without consent is prohibited, because such conduct constitutes degrading treatment, then Article 7 has wide potential application to many issues. Is research with children or incompetents legitimate if 'free consent' is given by a proxy? Is research in emergency settings permissible, on a theory that there is consent through the political process?

Finally, what are the limits of the concept 'experimentation'. To turn to an extreme example, but one relevant to the meeting of the IBC, may it be argued that when governments permit the test-marketing of new genetically engineered foods, pursuant to regulatory arrangements that monitor closely whether there are adverse effects, they are, in effect, treating consumers as research subjects? The null proposition tested is roughly 'the subset of the population that eats this food will be, some days later, medically indistinguishable from those who do not consume it'. Is consent necessary? Does labeling suffice to provide it?

There are extraordinary ambiguities in the concepts of 'research', 'experimentation' and the like, that the literature on research ethics has not securely answered.

The proper role of Article 7 is an important future issue in answering them. If Article 7 is given broad scope, then we must limit what we call research, so that, for example, changes in regional environmental policy are not deemed scientific experiments simply because policy makers are determined to study the effects of their actions, and derive generalizable knowledge from the inquiry.

Access issues may also be affected by regional agreements. For example, the proposed European Convention on Bioethics, in its June 1996 draft, has provisions that prohibit including persons incapable of personal consent in research projects unless stringent criteria

are met. One criterion for their inclusion is the familiar one that the research cannot be done without them. If the proposition being tested can be answered using subjects who can consent, then the incompetent cannot join. The proposed convention excludes incompetent persons with Alzheimer's disease from participating in research to determine whether a new drug can ameliorate their disease, if the drug's properties can be tested with Alzheimer's patients who have not lost their ability to consent. If this is a correct reading of the Convention, the question may well be asked, why should the most seriously afflicted be denied whatever benefits may flow from new therapy during the lengthy period that passes between initial drug tests and final product registrations?

Does it matter whether representatives of the Alzheimer community would agree to, or vehemently disapprove, the proposed restriction? One practical solution to the problem may be to say that if the drug is promising, it can be given outside the formal protocol. But why should that be done? Why not learn from each patient's experience with a drug?

The ethical problems may be further complicated by considering whether or not problems of patient accrual to research trials are relevant in deciding whether the research can be done on incompetent patients. With the revolution in biotechnology, there are large numbers of new approaches to difficult diseases, and there may, quite realistically, be too few patients available to test them all, at least for the indications most likely to give clear and quick data on drug efficacy. How, under the convention, does one analyze the situation where the research proposition can theoretically be tested on patients who have the capacity to consent, but such patients are much more difficult to locate because they are already involved in other clinical trials? One can imagine endless variations on this theme.

B. *National Law and Access Issues*

The scope of international obligations as they relate to access to experimental treatment may be uncertain, but nations have their own laws directed to these very same issues. These laws are, as one would expect, of different character. To illustrate, Article 54(1) of Hungary's Constitution echoes Article 7 of the CCPR; France has comprehensive legislation on human experiments; and the United States of America regulates them through a complex mix that includes federal (and some State) statutes, administrative regulations and common law rules.

There is, so far as the authors know, no single source that assembles all the relevant legislation around the world. See, however, Kelley et al. (1993) for an excellent, if only partial, compilation.

National legal treatment can adapt more easily than international rules to changing perceptions of the access question. In the United States of America, concerns about access have had a major influence on recent policies. For example, access concerns have had a dramatic impact on how the FDA evaluates AIDS medications, and FDA has stated it will apply similar fast track procedures to drugs for other serious diseases (Edgar and Rothman, 1990).

By statute and regulations, new concern has focused on problems of women's health (US Dept. of Health and Human Services (NIH), Fed. Register, 1995). Regulatory reformulation to permit emergency research without conventional consent is near conclusion (US Dept. of Health and Human Services (FDA), 60 Fed. Register 49086-49103, 1995).

FDA has already permitted IRBs to approve use of 'humanitarian use devices' for conditions affecting fewer than 4,000 individuals per year; and with no requirement from federal law that the patients' informed consent be secured. The devices are not FDA approved for safety and efficacy, and their use is not considered to be research, even though the hope is 'to encourage the discovery and use' of devices for rare conditions (US Dept. of Health and Human Services (FDA), 61 Fed. Register 33232-33248, 1996).

Finally, the research regulations were waived to permit the United States of America to give military personnel, without their informed consent, 'experimental' drugs to protect against chemical warfare attacks (Doe v. Sullivan, 938 F.2d 1370, D.C. Cir. 1991).

Whether access issues will have comparable impact on national policies elsewhere remains to be seen.

C. *Ethical Standards*

The Helsinki Declaration promulgated by the World Medical Association in 1964, and amended several times since, is the principal professional document concerning research ethics, although a large number of medical disciplines have their own professional guidelines. And, of course, a huge philosophical/ethics literature is directed to research ethics. Since the 1970's, and the publication of the Belmont report (Katz, 1996), ethics problems in research have most often been analyzed by the 'three principles' - respect, beneficence and justice - that the Belmont report analyzed. There is also substantial literature devoted to whether these principles, or their analogues, can be found in most cultural traditions (Gillon, 1994).

Turning to the Helsinki declaration, one must first stress its intent to provide professional ethics rules that harmonized with the Nuremberg Code, but provided as well additional ethical principles for topics that the Nuremberg code did not explicitly address.

There are, for that reason, many differences between Helsinki and Nuremberg. Among them, Nuremberg described research as a true partnership, based on the subjects' commitment. By contrast, the Helsinki Declaration stresses the patients' absence of obligation to continue his participation, if at any time he changes his mind.

The Helsinki document is unclear about most of the issues related to access. First, it states that a 'physician must be free to use a new diagnostic and therapeutic measure if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering'. Taken literally, this means that a physician who believes a new therapy works should not - at least as a matter of professional ethics - feel obliged to follow the set of rules that regulate drug and device testing. But these rules do limit his freedom to use his own judgment. After all, the regulatory authorities (FDA, etc.) will not even let the physician have the new drug, unless she consents to use it under guidelines that preclude mere personal judgment.

Although the Helsinki Declaration seems to favor access to experimental therapy if the physician believes it offers hope, and the patient agrees, the Declaration may be inconsistent on the point. Under Helsinki, the first principle of research ethics is that research proposals should be evaluated by a committee to secure its 'consideration, comment and guidance'. May the physician ignore the guidance? If not, the physician is not free when doing 'medical research combined with professional care' to use a new therapeutic measure as part of a research effort. His patient's access is blocked if the committee rejects his judgment, even if he has the drug, or indeed has personally invented the new medical device in question.

There is a possible reading of the Declaration that makes sense of the seemingly contradictory requirements. May the physician, faced with committee refusal to approve, say I will use the new therapy, but I will not do it as part of a research project? If it is not research, the committee need not be involved. If so, the situation illustrates the oddity that the professional ethics rules accord protections that are not triggered by risks to patients, but by the declared motivations of researchers. This is a very important problem, for the protection that research ethics provide require characterizing interventions as 'research'.

Second, the Helsinki Declaration has complex provisions on research in clinical trials. When medical research is combined with professional care, the Declaration states that 'the potential hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods'. The implication is that a clinical trial cannot compare a new treatment to a placebo if there exists some treatment that properly can be called 'the best current diagnostic and therapeutic method'. It is not self-evident why, if the best treatment is really very poor treatment, fully competent adults cannot consent to ignore it, especially if that will provide clear evidence of the efficacy of an entirely new approach (Nightingale, 1995). Indeed, paragraph three of the Declaration, if taken literally, would call into question many random clinical trials. It states that 'every patient - including those of the control group, if any - should be assured of the best proven diagnostic and therapeutic method'. How can one test a new unproved therapy when its use automatically deprives the subject of the opportunity to secure 'the best proven diagnostic and therapeutic method'?

(In discussions among members of the IBC, the consensus was clear that the Helsinki rules should not be read to preclude, in all instances, using placebo controls when there is a common standard treatment that is not satisfactory.)

Third, the Helsinki Declaration seems to require consent in all cases (Principle 9). When research is combined with professional care, however, and the physician considers it 'essential not to obtain informed consent', he should explain why in his protocol proposal. The implication is that the independent committee may approve his intention to act without consent, for otherwise, there would be little point in submitting it. Yet the criteria that might justify a committee in ignoring consent are not addressed.

Finally, the Helsinki Declaration does not deal explicitly with the problem of equal access for the legally incompetent. The principles voice special caution concerning research with persons who are in a dependent relationship (Principle 10) or are legally incompetent. The problem of assuring that these persons have access to potentially valuable treatments is not remarked upon.

The International Ethical Guidelines are much more comprehensive than the Helsinki Declaration. Most recently reformulated in 1993, they are drafted with attention to access issues, but on some key points they bridge resolution of the issues by using language that is adaptable to contradictory interpretations. Thus, Guideline 1 requires informed consent without qualification, and permits proxy consent by a 'properly authorized representative'. Yet the commentary suggests that, with respect to otherwise competent adults who are 'totally unfamiliar with modern medical concepts', the subjects' assent, coupled with approval by an independent ethical-review body, may suffice. It is a very important qualification given the Guidelines' intended audience in the developing world. Consent principles should not prohibit researching diseases found only in the developing world, among populations where individual 'informed' consent may be hard to secure. That principle should, however, apply equally powerfully to, for example, emergency research in the developed world, yet the Guidelines and Commentary do not address the problems as a general one.

Similarly, Guideline 6 seems to set out an absolute principle only to have its message blunted by the commentary. It states (as does the proposed European Bioethics Convention, *supra*) that incompetent persons should not be research subjects where the research 'might equally well be carried out on persons in full possession of their mental faculties'. Yet the commentary states that incompetent persons who 'have, or are at risk of, serious illnesses such as HIV infection, cancer or hepatitis, should not be deprived of the possible benefits of investigational drugs', at least if those drugs 'show promise' of therapeutic benefit. They are not proper participants in 'formal clinical trials', however, unless those trials are directed at the impairment that makes them vulnerable.

The Community makes no effort to defend these distinctions. Their rationale is not readily apparent.

In Guideline 7, the contradictory impulse is resolved in favor of access. Prisoners should not be denied experimental treatment for experimental therapy.

Guideline 10 recognizes that benefits and burdens of research should be equitably distributed, and calls both for the special protection of the vulnerable, and the availability of drugs to vulnerable people if they are made available to others' before they are fully licensed.

Conclusion

In the end, access claims force us to recognize that, for all the salutary impact the rules about medical research have had, they do not rest on any easily stated single principle, and the grounds and limits of their application in contexts beyond the traditional physician-patient relationship may be problematic. What activities constitute experimentation and research, and why are they special?

The practical problem the community concerned with research ethics faces is how to accommodate access problems by adjustments to the core rules - making appropriate exceptions to permit access when it seems compelling to do so. This is a difficult task because acknowledgment that principles claimed to be absolute are not really absolute threatens the whole enterprise. Still, it is virtually unthinkable that a body of practice that has had such a beneficial effect in regularizing research procedures should be abandoned because a few difficult problems.

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International Bioethics Committee

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