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Ethics in International Health Research: A Perspective from the Developing World

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Introduction & Background

The fact that we live in an unequal world with wide disparities in health and economic development is no surprise. Although the methodologies for evaluation of these inequalities and health outcomes may differ (Murray & Lopez 1996, Houweling et al 2001), they all indicate wide differences in performance of the health systems (World Health Report 2000) and wide global and regional inequities in economic status and health outcomes (Evans et al 2001). While some attribute these inequities to largely irremediable ecological and geographic factors (Sachs et al 2001), others see both threats as well as remarkable opportunities that can help overcome them (Yach & Bettcher 1998). The close correlation between these global disparities in health and human rights, has been highlighted by Benatar (1998). It is also quite likely that without the requisite safeguards, increasing globalization may further contribute to increasing inequalities in health, especially in those countries with marginalized populations and lack of participatory democracy. Health is the cornerstone of development and in the words of Chen and Berlinguer (2001); "good health is a cornerstone of economic progress, a multiplier of society's human resources, and, indeed, the primary objective of development". Public health programs are thus key in achieving these lofty goals in developing and resource-poor countries.

It is particularly in this context that public health programs and decisions need to be based on bedrock of evidence. While there are philosophical debates in the developed world as to whether economic considerations in health care are commensurate with individual patient rights and welfare (Emanuel 1998), the arguments for basing public health decisions in developing countries on the best available evidence are pervasive. Injudicious use of limited resources in such settings will inevitably lead to lack of improvement in the health status of the populace and therefore public health policy must be guided by appropriate research and leadership (Mann 1997a). The paucity of resources for supporting appropriate research in developing countries has also been the subject of much attention in recent years. The Global Forum for Health Research has pointed out that less than 10% of the world's research resources are earmarked for 90% of the health problems (GFHR 2000 Report). The way ahead to promoting a just distribution of the

fruits of research and global public goods is also through promotion of equity in health research and strengthening the capacity within developing countries to undertake relevant and much needed research (Mills 2001). The planning and execution of such research, be it basic bench-top biological or public health research, must be based on the fundamental principles of upholding human dignity and ethics. It is therefore not surprising that ethics forms the corner stone of research and has been the focus of much attention in recent years.

The context and historical background of ethical conduct and regulation of international biomedical research

Much of the recent debate and controversy in international bioethics has stemmed from the recent regulatory processes and international guidelines for the conduct of research. However, in order to understand the background one may need to refer to the genesis of these guidelines.

The basic principles of ethics in the conduct of human research stem from the Hippocratic model of practice (Hippocratic corpus 1923) which specified that "the physician will use treatment to help the sick according to his ability and judgment, but never with the view to injury and wrongdoing" and that "Physicians must take a habit of two things – to help or at least do no harm". Thus the focus was primarily on the physician's obligations and sense of morality rather than the rights of the patients who in turn, were expected to depose a high level of trust in their physician (Beauchamp & Childress 1994). With the advancement in medical knowledge over the centuries and the means at the disposal of the physician to achieve this, the need for a better paradigm of thought became evident. According to Claude Bernard (1927) the physician's obligation to achieve a constant improvement in outcomes by scientific enquiry must be balanced by the duty to protect the patient from the burden of experimentation, i.e. "the principle of medical and surgical morality consists in never performing on man an experiment which might be harmful to him in any extent even though the results might be highly advantageous to science. i.e. to the health of others".

The events around the Second World War with widespread atrocities committed by Nazi scientists and physicians under the guise of medical experimentation, brought the need to put forward a code of conduct for human research. The Nuremberg Code was the first such set of rules for the protection of human subjects in research and was put forward by a group of American judges who attempted to merge the concepts of Hippocratic ethics and fundamental human rights into a single code of conduct (Shuster 1997, 1998). While the Nazi experiments received considerable attention and widespread vilification, other atrocities and germ warfare experiments conducted by the infamous Unit 731 of the Japanese army received much less publicity (Harris 1998*, Kristoff 2001, Working 2001).

Although it is debatable whether the Nuremberg code had any impact on the conduct of human subjects research in the United States (Moreno 1997), it served to focus attention on the needs for protecting the rights of participants in such experiments and also formulated the fundamental right to voluntary consent. The task of taking the issue of human rights in biomedical research was taken a step further by the World Medical Association (WMA) at its meeting in Helsinki in June 1964 with the resultant declaration of Helsinki. The Helsinki Declaration underscored 12 basic principles underlying the conduct of human biomedical research and has subsequently undergone multiple revisions. Although the Helsinki Declaration laid down several fundamental principles for human subject protection, it was largely physician-oriented and did not directly address the issue of research in developing countries. These issues were taken up by the Council for International Organization of Medical Sciences (CIOMS), which proposed guidelines for international research in collaboration with the World Health Organization (WHO 1982). These guidelines were further amended in 1993 as the International Guidelines for Biomedical Research involving Human Subjects and are also undergoing revisions.

These aforementioned guidelines were widely publicized and recognized by agencies involved in human research, but their implementation and acceptance was largely a voluntary issue. This was highlighted by the furor and public outrage following the

discovery that medical researchers had deliberately withheld treatment from African American patients with Syphilis in Tuskegee, Alabama (Brandt 1978, Rothman 1982 & 2000, Fairchild & Bayer 1999) and the viral hepatitis research on children at the Willow brook State School (Giles et al 1969, Goldby 1971, Edsall 1971). Following the publication of these research studies, a national commission was established to develop principles and guidelines for human research and produced the seminal Belmont Report (1988). The Belmont report drew upon the existing Helsinki Declaration and highlighted three principles, namely respect for individual autonomy, beneficence and justice (Varmus & Satcher 1997). Others (Emanuel et al 2000), have highlighted seven basic requirements for ethical evaluation of a research project; namely an evaluation on the basis of social or scientific value, scientific validity, fair subject selection, favorable risk-benefit ratio, independent review, informed consent and respect for potential and enrolled subjects. Although these guidelines have remained the cornerstone of regulations for biomedical research, they have led to the development of other technical guidelines for the design, conduct and ethical review of research in recent years (ICMR 2000, WHO/TDR 2000).

Recent controversies in international research and their implications for regulation and guidelines

In 1994 the results of the first randomized controlled trials of intensive maternal and infant oral and intravenous zidovudine (ZDV) in USA and France by the AIDS Clinical Trials Group (ACTG) Study 076 were published (Connor et al 1994). These trials indicated a significant reduction in rates of vertical transmission of the HIV virus to infants from 25.5% to 8.3% at the time of the interim analysis, when only two thirds of the planned recruitment had taken place. The study was therefore stopped and the ACTG 076 regime soon became the standard therapy for prevention of mother-to-child transmission (MTCT) of HIV infection. Following the publication of these data, the WHO convened a meeting in Geneva to evaluate strategies for prevention of MTCT of HIV infection in developing countries. The panel of experts assembled at this meeting considered the intensive ACTG Study 076 regime far too expensive for introduction in developing countries and recommended the evaluation of simpler regimen including a

placebo arm in control populations (WHO 1994). Soon thereafter 18 trials of antiretroviral drugs were initiated in different parts of the world of which 15 used a placebo arm. Of the others, two were sited in the United States and one trial in Thailand employed an equivalence arm with full ACTG Study 076 regime. In September 1997 the controversy over the use of placebos in these trials became public with the publication of a commentary (Lurie and Wolfe 1997) and editorial (Angell 1997) in the prestigious New England Journal of Medicine. This was followed by a prolonged and acrimonious debate on the ethical aspects of such trials, with opponents of these trials equating them with the infamous Tuskegee study and proponents espousing a wide range of views ranging from moral outrage to the need for pragmatism and decrying the "ethical imperialism" of developed countries (Aaby et al 1997, Varmus and Satcher 1997, Semba 1997, Cooper 1997, Annas and Grodin 1998, Crouch and Arras 1998, Grady 1998, Glantz et al. 1998, C. Levine 1998, Bloom 1998, Levine 1999, Resnik 1998, Lie 1998, Schüklenk 1998, Thomas 1998, Del Río 1998, Brennan 1999, Coovadia & Rollins 1999, Nuffield Council for Bioethics 1999, Halsey et al 1999, Benatar and Singer 2000, Greco 2000, Schüklenk and Ashcroft 2000, London 2000, Bhagat & Nyazea 2000, Rothman 2000, Macklin 2001).

The controversy has not been helped by the intense polarization of views on these issues globally with many ethicists insisting that the trials violated the fundamental inviolability of universal human rights and researchers indicating the need for realism and a pragmatic approach to public health research in developing countries. The subsequent publication of the Report of the Perinatal HIV Intervention Research in Developing Countries Workshop (1999) was followed by a spate of indignant letters highlighting the inviolability of the statements made in the Helsinki Declaration and CIOMS guidelines (Omene 1999, Lurie & Wolfe 1999, Isturiz 1999, Greco 1999).

The debate has remained alive because of the relative intransigence of all concerned in this debate and the arguments put forward by both sides in support of their positions. Some ethicists refuse to budge from the fundamentals and see the entire issue of international health research through the looking glass of guidelines and regulations,

whereas others attempt to bridge the divide. Their chief requirement is that a single moral standard should govern all research on human subjects regardless of where and when the research is carried out. Most of the public health professionals and research scientists who appealed to the need for research in developing countries and the use of placebo controlled trials (Levine 1999) have largely focused on the issues surrounding HIV transmission. Not surprisingly, the voices and arguments of many of the developing world scientists and researchers seeking to expand the debate have been largely ignored. The statement of the Gambian government/ Medical Research Council joint ethical committee (1998) is the only public statement in this regards and attempts to enlarge the debate to the broader issues of public health. Perhaps a bit naively, others (Editorial Lancet 1997) have gone to considerable lengths to indicate that the dilemmas can be resolved by appealing to the fundamental principles "that doctors do no harm to patients, that doctors do their best for patients" and questioned the relevance of arm-chair philosophers and ethicists. The fact remains that doctors are every bit as human or inhuman as other inhabitants on this planet and come in all shades and colors. The recent guidelines for regulation of human experimentation must be seen in the backdrop of atrocities committed by doctors upon vulnerable subjects within recent memory. The highly controversial trials of induction of malaria in HIV patients (Heimlich et al 1997) and the trovafloxacin trial in Nigeria (Boseley 2001, Stephens 2000 & 2001) are two recent examples. Few also recognize that Radovan Kradzik, who stands accused of master minding the worst possible mass genocide in Europe in the post second world war era, is also a psychiatrist by training. Thus the regulation of human subjects research would require more than an appeal to basic human good and abject faith in the beneficence of the medical profession.

Concerns within the international sponsors of research on standards of ethical review and conduct of research

Since many of the HIV trials in question involved US funding agencies, these recent controversies led to a major review of the regulatory process for ethical review and guidelines for the conduct of biomedical research in developing countries by the US

National Bioethics Advisory Commission (NBAC) and other agencies (Moreno et al 1998). These guidelines have been recently revised and are mandatory for any international research projects requiring US Federal funds (McCarthy 2001). While these regulations set stringent criteria for the local ethical review process in developing countries as well as standards of care, the requirements offer relatively greater flexibility in interpretation than the existing Helsinki Declaration and CIOMS guidelines.

Concomitant with the pressure on regulatory agencies, there was intense pressure on the WMA to modify the Helsinki Declaration to make it more flexible and accommodative of realities of the research milieu in most developing countries (Levine 1999). The WMA agreement to revise the declaration was followed by intense lobbying and pressure from different quarters (Brennan 1999, Ramsay 1999). The fifth and the latest amendment to the Helsinki Declaration was thus ratified at the 52nd WMA meeting in Edinburgh in October 2000 and has subsequently led to much debate in different quarters as to its implications for research in developing countries (Levine 2000, Loff 2001, D'Alessandro & Boelaert 2001, Macklin 2001, Emanuel 2001, Raja 2001). Although there has been no concerted move to reach broad consensus on various aspects of these guidelines on the part of the WHO, it has lent its support to supporting these initiatives and achieving consistency (Wikler and Pang 2000). The newly established Global Forum for Bioethics in Research is another move in this direction and aim to provide a joint platform for researchers, funding organizations and bioethicists to exchange views and develop consensus. Two international Global Forum meetings have been held to date in Bethesda (Hofman 1999) and Bangkok (Loff 2000) and another meeting is planned for the Gambia in November 2001.

Concerns from developing countries

The background and the events surrounding the Helsinki Declaration clearly indicate that its genesis lay in the atrocities surrounding human experimentation in the second world war. Although attempts were made to address the issues of regulation of research in developing countries (Angell 1988, Barry 1988, Prout et al 1988), it is debatable as to how much influence these declarations and guidelines had on the conduct of research in

developing countries. It was really not until the controversy surrounding the HIV trials in the mid-1990s that the issues of research in developing countries came to the fore. However, the response since has not been as inclusive of the wide range of opinions from the developing world. It can also be argued that the while the concerns about research in developing countries have brought a welcome focus on this long-neglected area, the focus has been on regulatory issues rather than the basic problems that underlie the inequities in health and human rights in developing countries.

It is important to point out that the revised Helsinki Declaration was largely drafted by a team of writers from developed countries and although a larger consultative process was undertaken, it primarily consisted of professional medical associations in developed and developing countries, who neither represented the broad community, nor public health interests. There was no consultative process with a host of medical research councils in developing countries as to the applicability or potential conflict with existing regulations. Not surprisingly, at its council meeting in May 2001, the WMA agreed to investigate the guidelines further as the changes made "might be in contravention of some countries' ethical guidelines" (Human 2001).

This process of imposition of a doctrine of conduct of research trials has been labeled by some as a form of "Ethical Imperialism" (Mbidde as cited in Macklin 2001) and others as a condescending approach to developing country researchers and ethics review committees (Gambia Government/MRC JEC 1998). Still others have lamented the fact that although the current debates on research in developing countries center around the technical processes of ethical review, study design and standards of care, they forget to address the underlying issues of economic deprivation and gender inequities (Moazam 2000).

Current ethical issues of concern in international research

The issues relating to biomedical research in developing countries is complicated by the fact that much of the debate had centered around sponsored and international research, whereas a large percentage of such research is indigenously sponsored and regulated by

local rules and guidelines. In many cases these guidelines are every bit as thoughtful as international guidelines such as the CIOMS and Helsinki Declaration, and importantly, reflect local consensus and agreements. The recent guidelines of the Indian Council for Medical Research (ICMR 2000) for the Ethical Conduct of Biomedical Research are the product of an extended process of consultation and public debate over several years, and are an example of how such a process can facilitate the ethical conduct of research. Importantly, whenever such guidelines are developed or ratified, they are also owned by the local research community and public health leadership, and are thus relatively easy to implement.

In other parts of the developing world the capacity to undertake such a process of developing local guidelines may neither exist nor deemed necessary in the presence of a plethora of international guidelines. Although the Helsinki Declaration and CIOMS guidelines do not have legal binding on nation states, they do have moral validity and ostensibly influence research policy by most international funding agencies and pharmaceutical industry. It is thus inevitable that these existing international guidelines will continue to form a cornerstone of research ethics in much of the developing world. The key issue is one of the application of the true spirit of these guidelines and a contextual interpretation of their recent amendments. The current debates seem to be centered on the specifics and semantics of terminology and have largely focused on individual rights rather than public good. The latter concepts of public health policy and decision-making are based on a larger objective utilitarian assessment of greater public good rather than individual subjective assessments (Bentham 1996, Mann 1997). It is in this field of public health that the application of the broad principles of public health ethics lags far behind that of individual ethics (Roberts & Reich 2001). It is not the intent of this paper to extensively debate all the controversial aspects of the recent amendments to the Helsinki Declaration and the CIOMS guidelines, but to discuss the three most contentious issues that have led to much debate. These include the sections relating to community benefits or prior agreements pertaining to research outcomes, the use of placebos and the standard of care required for control populations participating in the study.

Several additional aspects pertaining to the design and conduct of research in developing countries do merit some comment. The first pertains to the need for the research to respond to community needs and national priorities. Clearly the gross inequity in the distribution of the world's resources for research into issues of concern to developing countries is a glaring injustice that merits resolution (Global Forum for Health Research 2000). Undoubtedly there are truly international or global issues affecting the development of research questions, this process of must be firmly grounded in a national process of priority-setting within developing countries (Margetts et al 1999). With much of the developing world caught in a vicious spiral of growing debt, structural adjustments and increasing poverty (Olweny 1994, Bhutta 2000, 2001c), the larger and more difficult challenge is to involve the communities themselves in the determination of these research questions and the link of the research to their development. This process may require external expert consultations to evaluate the scientific merit and "clinical equipoise" in relation to the research question (Freedman 1987). Such a participatory process with the community is a continuum ranging on the one hand from community consultation in protocol development, appropriate information disclosure and informed consent, protection of confidentiality and right of dissent, to their involvement in the conduct of research as well (Weijer & Emanuel 2000, Editorial Lancet 2001). The important aspect here is one of a participatory process. Although "cultural relativists" (Macklin 1999a) may counsel us to respect local customs and beliefs, community traditions must never be taken to indicate that human rights and fundamental ethical principles are also relative (Thomasama 1997). To illustrate, although the processes of obtaining informed consent may vary according to local customs, the fundamental principle of informed decision making by research participants remains inviolable (Macklin 1999b, Wendler 2000).

*It must be stated that this framework of individual or largely pertains to public health and applied research. It is also evident that as the world shrinks many research projects may focus on broader regional priorities rather than issues of a narrow local interest. It is thus imperative that a reasonable means and terms of engagement be found that respond to community needs and concerns (Wilson 1999). We would place this process squarely

in an environment of participatory democracy and freedom of expression. Not only is an autocratic and despotic leadership likely to pawn a nation's interests and rights for personal gain, such governments also succumb more readily to the influence of transnational industry interests. The case of the controversial Trovan® drug trial for meningitis in Nigeria is a case in point, when the military government approved the trial without consulting any of the academic leadership in the country, nor assuring any ethical safeguards (Boseley 2001, Stephens 2000 & 2001). The existence of such a participatory process of decision-making may also enhance the prospects of achieving a fair distribution of a nation's health and biomedical research resources can be achieved, with allocations to both public health researches with tangible benefits, as well as to basic and biomedical research with relatively nascent future gains.

If a country's' health research system could be regarded as the "brain" of its health system, then ethics would constitute its "conscience". It is imperative that such health research systems, broadly defined as all institutions and individuals involved in health and biomedical research within this paradigm, function to the highest aspirations of ethics and distributive justice. This framework thus places ethics at the very core of a country's programs for health, equity and development..

i. ***Prior Agreements and Benefits of Research***

The issue of prior agreements and assurances of benefits of the products of research has received comparatively less attention than the practical aspects of protocol development and study design (Hardy 1996). The commentary on Guidelines 8 and 15 of the CIOMS guidelines (1993) explicitly state

"As a general rule, the sponsoring agency should agree in advance of the research that any product developed through such research will be made ***reasonably available*** (emphasis added) to the inhabitants of the host community or country at the completion of the successful testing. Exceptions to this general requirement should be justified and agreed to by all concerned parties before the research begins"

The most recent revisions of the Helsinki Declaration (2000) take a less stringent position but declare that "Medical research is only justified if there is reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research". While the most recent guidelines of the NBAC (2000) also do not make "availability" a pre-requisite for research, they do regard such a move on the part of the researchers, as laudatory. Others have criticized the CIOMS guidelines as being rather soft and indicated the need for explicit agreements and identification of funding prior to undertaking the research (Annas & Grodin 1998).

Taken in its most simplistic interpretation, this requirement would preclude any large-scale public health research in developing countries unless these assurances could be provided. The proponents of this approach defend it by indicating that application of this principle would avoid unnecessary and curiosity driven research and undue exploitation of vulnerable populations and that underdeveloped communities exposing themselves to the risks of research must at the very least, be assured of access to the fruits of the research. According to Emanuel (2001) "reasonable availability is an attempt to counter the poor bargaining position of the populations in developing countries by creating a mechanism to ensure that they also receive benefits from the research".

Admittedly, these assured availability agreements only apply to a narrow band of drugs, vaccines and other products. It clearly cannot apply to either phase I and II drug or vaccine trials, nor epidemiological and social science research. The benefits of participation in the research may extend well beyond the narrow definition of end-products as there may be other significant improvements in the health care system as part of the project. There is always the nagging possibility that the assurances of such benefits may offer inordinate inducements to poor and impoverished populations and thus represent another form of exploitation. Moreover, a broader definition of benefits other than the product of research may be required, as mere availability of a product within a dysfunctional health system, is no assurance that it will get to the people who need it most. In many developing countries impediments to the health systems or political doctrine may demand that either all or none of its citizens should have access to a

particular product. Given these considerations, it may well be impossible to make an economic argument for the independent pharmaceutical industry to pursue research of relevance to developing countries.

It can also be argued that the stringent application of these criteria and guidelines within the limited indigenous resources in most developing countries might make it almost impossible to provide such assurances, thus effectively stopping much needed public health and epidemiological research, which is often targeted to precisely generate the information that might influence public health policy. To illustrate, much of the epidemiological information on the prevalence of Hepatitis B in Pakistan was derived from population-based sero-prevalence studies almost 15-20 years ago (Khadim et al 1980, Malik et al 1988) with the precise objective of securing information that might lead to preventive programs. Although following the publication of these data, routine screening in blood banks was started in the early 1990s, the introduction of hepatitis B vaccine in the national expanded program for immunization has taken much longer. Pakistan will be the first country in South Asia to introduce Hepatitis B in its childhood EPI program from July 1, 2001. It is also important to point out that the costs of products are not static and that the same hepatitis B vaccine which cost almost $ 100 per dose in the early 1980's now costs under one $ per dose, thus making it possible for health systems to afford it. It can thus be argued that had the data not been generated and concerted pressure not been exerted on policy makers on that basis, that national hepatitis B vaccination program would not have materialized. Sometimes the decisions and agreements to introduce interventions within health systems need to be seen in the larger context of time taken to evolve an affordable and sustainable health care strategy, and should not be made pre-requisites for research. However, placing these issues at the forefront of research planning especially if the research has international sponsorship, can help expedite this process.

The ground breaking way in which research on Hepatitis B (Gambia Hepatitis Study Group 1989) and *Haemophilus influenzae* type B (Hib) vaccines (Mulholland et al 1997) was undertaken in the Gambia points the way. A participatory process involving donors,

researchers and the Gambian Ministry of Health ensured that the vaccination program with these vaccines could be sustained well beyond the trials. In contrast the evaluation of Hepatitis A vaccination in Thailand (Vimolket et al 1998) was not accompanied by any such agreements or plans to introduce the vaccine, neither are such agreements part of the current evaluations of the newer typhoid (Lin et al 2001) and pneumococcal conjugate vaccines in other parts of Southeast Asia and Africa (Mulholland 2001).

Another important issue that merits consideration in the debates around the availability of the products of research is the soundness of the research findings. How many trials are needed before one can conclude with certainty that a drug or vaccine works? If several are needed then clearly the definition and time-line of availability of any particular product would need to be flexible. It can also be argued that the premature introduction of such interventions as a part of prior agreements, immediately following the conclusion of the trials, may result in actual harm to the community. To illustrate, although the high-titre Edmonston-Zagreb measles vaccine was found to be more immunogenic, the delayed increase in mortality in vaccine recipients was only appreciated later (Knudsen et al 1996). To extend the argument further, the context of the availability of the products of the research within the health systems must be seen with regard to the capacity of the system to deliver and monitor the interventions. Had the rotavirus vaccination been rapidly introduced in developing countries with rudimentary adverse events reporting systems, it is more than likely that the serious adverse effects of intussusception (Murphy et al 2001) may not have been recognized in time.

The issues of the responsibilities of the researchers are also not related to the narrow spectrum of the research question and trials. Trials evaluating a reduction in childhood mortality due to malaria by the use of insecticide treated bed nets may actually predispose the population to an increased risk of delayed morbidity and mortality due to malaria as natural immunity may diminish with decreased exposure, which then takes place when the participant can no longer afford the bed net treatment even though it is effective (Snow et al 1995). This may necessitate prolonged follow up and observation. Following the widely acclaimed Gambian Hib vaccination study (Mulholland 1997), researchers are

still following the children and local patterns of Hib disease in order to assess any risks of increased susceptibility to invasive Hib disease in later life.

It is therefore evident that the concept of "reasonable availability" does not settle the issue of responsibilities to the community. In its narrowest definition, it may be interpreted to indicate a simple assurance of the availability of a research product within the local market and expanded to include responsibilities to the care and well being of the community for a very long time. The latter requirement may place an inordinate burden on both governments and other sponsors, effectively stopping all large-scale trials in developing countries, whereas the former situation may open many a vista for exploitation. The truth probably lies somewhere in between, with a broader interpretation of responsibilities and potential for community participation in weighing the merits nd demerits of participating in the research.

Recently Emanuel et al (2001) have expanded the arguments to include several pre-requisites for an exception to the "reasonable availability" requirements of the CIOMS guidelines, provided that the study addresses important local health problems, the population's agreement to participate has been obtained in an open and participatory manner and that the risks of participation in the study have been minimized. These pre-requisites include

- Local capacity development for health services, research and ethics
- Provision of additional health services
- Provision and development of general public health measures
- Development of long-term collaboration
- Sharing of financial rewards or intellectual property rights with the study population

ii. Standard of care and the use of placebos

A major issue in the recent controversy surrounding the HIV trials in developing countries was the use of the placebo arm instead of ACTG 076 triple therapy, which was

at that time the newly established standard care in developed countries. The recent revisions of the Helsinki Declaration (2000) state clearly in section 29 that

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

Although many have passionately argued in favor of retaining placebos as the most efficient means of obtaining the requisite scientific information (Varmus & Satcher 1997, Levine 1999), their overall use in health research and therapy is probably overstated (Hrobjartson & Gotzshe 2001). Temple & Ellenberg (2000a, 2000b) argue convincingly that placebos are essential when the course of disease may be variable. The most pervasive argument supporting the continued use of placebos is perhaps efficiency and economics. If journals were willing to accept manuscripts with quasi-experimental designs and funding agencies willing to support studies for longer durations, several alternatives to placebo designs can be envisioned. The recent controversial placebo controlled trial of synthetic surfactant Surfaxin® in South America offers an interesting contrast (Okie 2000, McCarthy 2001, Brower 2001). The sponsors of the research Discovery Laboratories (Doylestown, PA, USA) chose the placebo arm for reasons of efficiency and reduction of research costs, even though the surfactant had clearly been shown to be effective in previous studies in developed countries and is well established as the standard of care. In contrast, in a similar study in Pakistan between 1995-1997, researchers chose to evaluate the efficacy of surfactant in treating neonatal RDS by treating all eligible infants and preferred to use used historical rather than concurrent controls (Bhutta et al 1999, 1995). While it is likely that the latter design may have been less powerful scientifically, it yielded sufficient information on the efficacy and cost-effectiveness of surfactant therapy in the local population, to allow its incorporation in the regular treatment protocols. It can also be argued that given the 50% reduction in mortality observed in the latter study, it would have been ethically questionable to put a potential control group of infants through the unnecessary and higher risk of death. Thus

in the wake of available scientific evidence, the scientific rigor and lofty ideals of a placebo controlled design can be balanced against alternative models of scientific enquiry which though longer and more expensive, are ethically sound.

Taken at its face value, although the Helsinki Declaration does not clearly specify, the standard of care must be seen in the context of the study location and can be variably interpreted. It can be interpreted as the *global* standard of care rather than a *local* existing standard (Macklin 2001) or a general standard of care in the research setting (NBAC 2000). The recent ICMR (2000) guidelines indicate that the comparative standard must be "the highest attainable and ***sustainable*** local standard" (emphasis added), whereas others (Benatar & Singer 2000) have expanded the definition of standard of care to include several additional aspects such as

- Provision of care by a research team with equivalent qualifications, training and expertise as developed countries
- Research undertaken by a team with the same culture and language as study subjects so as to assure effective communication and informed consent

This aspect alone has been the subject of much rancor and debate and highlights the wide disparities that exist in health and economics globally. Some researchers and developing country scientists (Gambia Government/MRC JEC 1998) have put forward strong views that given the abysmal state of health and facilities in many developing countries the local therapy for HIV infection may well be "nothing". In such circumstances

"there must be something better to offer than nothing, for the notion of doing nothing to help is repellant to everyone. Thus feasibility studies are needed to compare interventions under local conditions with current standard local therapy, even if that standard is 'nothing'".

Others have questioned the very notion of a global standard of care in that what constitutes a standard therapy in one health system with profligate expenditure on medical practice based on defensive medicine, may be totally inappropriate in another system with limited resources (Benatar & Singer 2000). One could argue instead that these decisions be based instead on the performance of particular health system. Given the findings of the recent World Health Report (2000), perhaps the French standards of care should be emulated world wide. The argument that the standard of care set in developed countries with widely different social and support structures is the normative standard fro the world, is tenuous at best. To illustrate, for decades, the standard of care for diarrhea and dehydration in the West consisted of intravenous rehydration. A strict imposition of this comparative standard would have neither allowed the studies that saved thousands of lives in refugee camps in Bangladesh (Mahalanabis et al 1972), nor prevented the terrible tragedy of cholera deaths among refugees in Rwanda (Heyman 1997). The world owes a tremendous debt of gratitude to the development of protocols for the management of acute respiratory infections among children in developing countries. It can be argued that none of these developments could have taken place had the comparative standard of care of the treatment of pneumonia in the West with injectable third generation cephalosporins. By the same token, although artificial feeding of infants born to HIV positive mothers is the standard in the West, encouraging this practice in Africa would kill infants due to diarrhea much faster than HIV would.

A recent landmark study in India makes an interesting case in point (Bang et al 1999). Dr Abhay Bang who leads an NGO in rural Maharashtra was confronted with extremely high neonatal mortality in this rural community on Gadchiroli. Given the paucity of health services and referral facilities in that area, Bang and colleagues undertook an evaluation of domiciliary neonatal care with community-based health workers administering oral trimethoprim-sulfamethoxazole and twice daily gentamicin to sick newborn infants with suspected sepsis. They used a control population for comparison and were able to demonstrate a 72% reduction in neonatal mortality using this approach. This study would have raised enormous ethical questions by most existing standards. It employed a control population and also used an experimental protocol in a situation

where the national standard of care for suspected neonatal sepsis was intravenous antibiotics and supportive care. Bang and colleagues went through an extremely elaborate scientific and ethical review process involving national experts and the ICMR prior to the initiation of the study and were also able to get community concurrence to participate in this study in a situation where even the national "standard of care" was not available to the participants. The benefits of the study on the local populace (in terms of improved neonatal survival) and its impact on national and global programs for newborn care have been enormous (WHO and Save the Children 2001). Taking an extreme position on the issues of standards of care would have required that the study only be conducted with a control arm receiving neonatal intensive care and expensive intravenous antibiotics, neither of which are sustainable in even urban settings in India. The study could not have taken place at all. The Gadchiroli trial vindicates the position of public health researchers that each developing country deserves the chance to develop health care interventions that suit it socio-cultural and economic means. Such projects form the foundation stone for a gradual and progressive improvement in the health status of the population. It is blatantly unfair to paint the entire family of health researchers as self-centered, myopic individuals who hold the value of science higher than human rights. The history of global progress in health, especially within developing countries, is studded by myriad examples from researchers who devoted their lives to the study of health and disease, often living and working within the populations they served. They and the communities they serve, are often better placed to judge what ethical standards should apply to a given situation and at the very least, deserve a fair hearing. This involvement by consumers and communities in the design and conduct of clinical trials has been lauded as the way forward in research within developed countries (Editorial Lancet 2001).

The aforementioned examples aside, it must be stated clearly that the safeguards and guidelines currently in place were largely devised to prevent undue exploitation of vulnerable populations and developing countries. These must be applauded and supported ensuring that they do not impede much of the requisite research into issues of public health priority. The Bangs of this world must be supported in the work they carry out with the full confidence and support of the communities they serve. On the other hand

clearly unscrupulous and opportune research which exploits the vulnerability and want of a given population, must be condemned. The case of the Trovan® drug trial in the midst of a meningitis outbreak in Nigeria (Stephens 2000) and the induction of malaria in HIV patients (Heimlich et al 1997) are examples where the need for ethical guidelines and minimal universal ethical standards for research becomes absolute.

The way ahead for ethics in international health and research

Would the absolutists in this Ethics debate be happy to see the status quo continue rather than sincere attempts to improve matters within available resources and time frames? The existing global inequities in health and resources are real and mere rhetoric will not change the situation. Just taking the situation of perinatal health and AIDS further, an estimated 3000 newborn deaths take place every day in the Indian subcontinent due to lack of basic newborn care (Bhutta 2001c). It is also estimated that more than 15000 cases become positive with HIV every day (Ainsworth & Teokul 2000). Both these conditions are largely linked to poverty and deprivation. Is it ethical to do nothing while we wait for ideal circumstances and dramatic socioeconomic changes? There is a real need to continue to strive to achieve true global equity in health and economics, but at the same time put our collective wisdom together in achieving these goals in an incremental process that ranges from individual practice to public health policy (Alvarez-Dardet & Ruiz 2001). Research remains the foundation stone for generating the evidence on which we determine public health policy. It is important to focus attention on the need for more research in developing countries and the need to see such research in the light of public good and benefits, especially for deprived populations within these countries.

Although recent debates on the ethical dilemmas of health research in developing countries have focused on the semantics of language and requirements, and lamented the polarization of views (Schuklenk 2000, Macklin 2001, Brower 2001), many do see a silver lining in all this. At the very least the debate has focused attention on the needs of developing countries and the vast inequities health and human rights. A pragmatic approach towards addressing these issues would necessitate several cogent measures aimed towards bridging the gaps. These include

1. **Linking issues of health and research with those of equity.** If the fundamental basis of research in developing countries is to improve the health status of the population and reduce the equity gap, then application of the principles of bioethics to the process will greatly help in addressing them. It is time to put ethics at the very core of the development and equity debates (Leon & Walt 2000, Benatar et al 2001, Fabienne & Evans 2001). As indicated by Singer & Benatar (2001), the inequities in global health and resource allocation are incompatible with the lofty goals of justice and no regulations or guidelines alone can overcome this.

   There is growing concern over the relationship of globalization of the world's economy and structural adjustments with increasing poverty and economic disparity in many developing countries (Wakhweya 1995, Bhutta 2001b). While recent agreements on general trade and tariffs, such as GATT, TRIPS, TRIMS etc have the potential of stimulating global trade and growth, there are major concerns on the potential impact of these new global regulations. It has been noted that these global regulatory changes, especially when coupled with health sector reforms, can have a negative impact on public health facilities and essential services in developing countries (Faunce & Drahos 1998, Balasubramaniam 1999). In a blistering attack on recent donor-led programs and approaches in Africa, (Save the Children & Medcat 2001), it has been noted that health systems in several countries has virtually collapsed. There are major concerns about globalization and imposition of international regulatory processes by the World Trade Organization (Price et al 1999, Pollock & Price 2000) to accelerate privatization of health services, which may further reduce public health coverage, especially to those below the poverty line (Moses et al 1992). These issues clearly have major implications for the ethical conduct of research in developing countries, especially when the research fails to address underlying issues of poverty, deprivation and inequity.

The lofty ideals of achieving ethical and appropriate health research can only be achieved if we put ethics at the very core of the global development debate. The partnerships that one can envision in the expansion of the role of ethics in global public health and research include all current stake holders, and extend to the role Industry can play in reducing the inequity underlying much of the ethics debate. The remarkable success of the Ivermectin development and drug donation program in Africa (Etya'ale 1998) is one program that gives us a ray of hope that one day the ethical debates on the appropriate treatment of AIDS among those in need will not be necessary. At the eve of the United Nations special session on AIDS, it has been pointed out that not just a minority, but that the entire "Earth has AIDS" (Berwick 2001). There are over 36 million people afflicted with AIDS globally and in some parts of the world such as South Africa and Bostwana, between 20-36% of the entire population is infected with HIV. Of the 3 million people who died of AIDS in the year 2000, a staggering 2.4 million (80%) were in Africa. Irrespective of the debates for particular forms of HIV infection and AIDS therapy in developing countries, in a hypothetical argument with all concerned, Dr Berwick of the Institute of Health Care poignantly argues the cases for international solidarity and provision of free anti-AIDS medications by stating

"The Earth has AIDS and therefore for now, we all have AIDS. Therefore, we are taking one simple action that will save millions and millions of lives. We choose to do it, together, and we will use the intelligence of our own forces to figure out how to make it possible, while preserving the futures of our companies".

Idealistic or naïve as this view may be, it helps summarize the philosophical divide in international health and research. It is hoped that an application of ethical principles to health and health research may help in bridging the gap between idealism and realism. Just because we live in an unjust world should not hold us back from the goals of practicing 'just medicine' and undertaking health research that forms its basis. The ethics debates surrounding AIDS research in developing countries should not be seen in isolation of the controversy

surrounding allegations of exorbitant profit taking on AIDS drugs by Industry giants (Peterson 2001, Bluestone 2001).

2. **Local Capacity Development**: Consonant with the participatory models for developing research priorities which address inequities (Olweny 1994, Edejer 1999), there needs to be a move towards strengthening models for ethical review of research, which also lead to local capacity development. The days of colonial models of "postal and parachute" research as well as "annexed sites" are over (Costello & Zumla 2000), and must be replaced by strengthening of research partnerships and capacity development. This capacity for undertaking research must also be extended to the strengthening of capacity to undertake ethical review of the planned research and its conduct by strengthening partnerships and capacity development. However, international and regional networks or partnerships in bioethics are no substitute for development of local capacity. In the words of Abdallah Daar (2001)

   "So long as all the ethicists are in the North and the South is just the recipient of ethical principles, nothing will change!"

   A review of the existing capacity in bioethics and ethical review of research in developing countries reveals major gaps (Kaas & Hyder 2000, Hyder & Nadeem 2001) and is one of the major reasons for exploitation of vulnerable populations. The training in bioethics within undergraduate medical education and postgraduate training programs must be strengthened, as must the curricular content of public health training programs. Given the glaring gaps, this will require a major investment in manpower and a completely new approach to the teaching of bioethics. The recent NIH-Fogarty training programs in Bioethics are a wonderful example of one such initiative. These grants provide substantial support towards the development of training programs in bioethics and international research ethics in both developed and developing countries. These training programs in bioethics have also been coupled with several regional

training workshops on Ethics and international research in Africa and Asia (Thankappan & Cash 2001), with an exponentially increasing global demand for the same. We need several such initiatives from as many quarters as possible, including from centers of excellence within developing countries. Singer & Benatar have recently called for a Global Alliance for health ethics (2001) on a model like that of the International Clinical Epidemiology Network (INCLEN).

The need of the hour is however, to undertake take the capacity building as a bottom-up approach focusing on strengthening local capacity and manpower development. Instead of a blanket imposition of regulatory requirements, there must be an evaluation of needs and gaps and development of innovative training models in ethics that are cost-effective and sustainable. Although the digital gap is real, virtual learning and exchange of information on the internet is here to stay. We must capitalize upon the opportunity that this technology provides for a wide range of learning opportunities and education in ethics. More importantly, this can also provide a mean of disseminating information on ethical principles within key research areas such as vaccination research, HIV therapy, reproductive health, social science research etc. A unique opportunity that may jump start capacity development is by linking developed and developing country Ethics Review Committees in consultations on common protocols and a "hybrid review". This learning process is always bi-directional. We believe that this may prove to be of great educational value to both developed and developing country ethical review committees (Bhutta 2000b) and may serve to provide much cultural empathy and understanding of diverse communities and cultures. There are clear cost implications for the development and sustainability of ethics committees in developing countries. Current models of research and external grants completely fail to recognize the integral role of ethical review and overview within projects and the ethical review process is regarded as more of a hurdle rather than an essential part of the research. An allocation of resources within research projects for the ethical review and oversight of research will help many developing country institutions to sustain these initiatives and improve its quality.

3. **Working towards a True Global Consensus and Ownership:** There is an urgent need to include all nation states in the broader issues and debates on ethical principles of research within the existing health systems. To date these debates have largely remained within the close-knit circle of ethicists or researchers. It is time to take these to a larger platform to facilitate their adoption and ownership by developing countries. Although the creation of the Global Forum for Bioethics in Research is a welcome move in this direction, it needs to expand further to include all key constituents and representatives from developing countries. The World Health Organization is the logical platform to address issues that require global consensus and agreements. The recent WHO-sponsored consultative process on the ethical issues surrounding HIV vaccination trials, is an illustration of what can be achieved through such a process (Guenter et al 2000, UNAIDS 2000). This recommendation is not to enforce upon WHO a role in the governance of global ethics, a role that it may neither have the capacity nor resources to fulfill, but to put it firmly as one of its core responsibilities in developing international health and research policies in partnership with other member states (Yach 1997, Kickbusch & Quick 1998, Kickbusch 2000).

4. **Future Ethics:** One can safely predict that ethics will assume center stage in the next few years in both developed and developing countries (Loff 2001, The Economist 2001), especially as the issues of human genomics research and biotechnology move to the forefront (Greely 2001). These issues largely pertain to those of cloning, and genetics research. While these concerns are currently at the core of ethics debates in developed countries (Collins 1999, Singer et al 2001), most developing countries are largely excluded from this process. The WHO has taken a major step in this direction by commissioning a report and multiple consultations on "Genomics and World Health" in 2001. This report follows on the heels of the Daar and Mattei report (1999) on the ethical aspects of cloning and biotechnology.

> The next logical steps would be to expand the debate from the narrow spectrum of ethics and genomics to the global opportunities that genetic engineering and biotechnology may bring in their wake, as well as the potential of increasing inequity. The ethical issues that surround the issues of patenting the human genome (Drahos 1999) and potential exploitation of genetic pools in developing countries (Hui 2000) are but early indications of the dangers that lie ahead. At the same time the dangerous inroads of modern biotechnology into traditional agriculture, vividly elucidated by the terminator seeds produced by Monsanto, must be forestalled (Singer & Daar 2000). The challenge would be to tackle the ethical aspects of this technological leap well before the world gets mired in further controversies.

In summary, bleak and confusing as the field may be, the last few years have been a watershed in international bioethics. While the debates are furious and acrimonious, they have served to push the ethical issues surrounding health research in developing countries into the limelight. The challenge before us is to develop a sound plan for expanding the ethics debates to embrace the larger issues of global equity and justice and to make the process as participatory and democratic as possible. It is critical to link issues of health, health research, ethics and equity as vital components of the same equation. The actions required to move ahead in this field include a concerted program for capacity development within developing countries for bioethics, linking issues of health research to addressing community needs in a transparent and participatory process, as well as increasing communication between developed and developing country scientists and ethicists; the clear goal in all these activities must be the reduction of global inequities. This may take time, but is the only way to bring about true change in the ethics of international health research and not mere cosmetic and superficial debate on the language of regulations.

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