ORIGINAL ARTICLE

Who is my brother's keeper?

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Clinical and research practices designed by developed countries are often implemented in host nations of the Third World. In recent years, a number of papers have presented a diversity of arguments to justify these practices which include the defence of research with placebos even though best proven treatments exist; the distribution of drugs unapproved in their country of origin; withholding of existing therapy in order to observe the natural course of infection and disease; redefinition of equipoise to a more bland version, and denial of post-trial benefits to research subjects.

These practices have all been prohibited in developed, sponsoring countries, even though they invariably have pockets of poverty where conditions comparable to the Third World prevail. Furthermore, the latest update of the Declaration of Helsinki clearly decries double ethical standards in research protocols. Under these circumstances, it does not seem appropriate that First World scholars should propose and defend research and clinical practices with less stringent ethical standards than those mandatory in their own countries.

Recent years have witnessed frequent reports of less stringent ethical standards being applied to both clinical and research medical practices, for the most part in the field of drug trials and drug marketing, initiated by developed countries in poorer nations. Still more unsettling, a number of articles have endorsed the policy of employing ethical norms in these host countries, which would be unacceptable to both the legislations and the moral standards of the sponsor nations. Also, these reformulations often contravene the Declaration of Helsinki or one of its updates. This paper is not so much concerned with the actual practices, which have been subjected to frequent scrutiny and publicly decried when gross misconduct occurred. Rather, my concern relates to the approval and support such practices have found in the literature on bioethics from authors who might be expected to use their energy and scholarship to explore and endorse the universalisability of ethics rather than to develop ad hoc arguments that would allow exceptions and variations from accepted moral standards. To this purpose, issue will be taken with arguments in three fields: medical and pharmaceutical practices, research strategies, and local application of research results.

Quinacrine is a drug which in its country of origin is listed as "unapproved", and therefore cannot be employed as a female sterilising agent. Nevertheless, it has been introduced into Third World countries on the basis that the demographic benefits by far exceed the potential side effects, even when these include drug-induced cancerous growths. Under the title, "Good enough for the Third World", Cooley has published a defence of employing unapproved drugs in developing countries, starting off with the statement that a drug with "ill side-effects" is a lesser evil than no treatment at all for life-threatening diseases.[1] An argument of this kind, however, needs to be validated by those involved, not by outside observers.

To bolster such a lenient view towards unapproved drugs, a quasi-utilitarian principle is introduced: "An act is normally right for an agent only if the agent, after proper consideration, believes that it will produce at least as great utility as any alternative to the act".[2] An admittedly "agent-centered relativity" of this sort erodes the principle of patient autonomy and is especially suspect in intercultural relationships were agent and subject differ in their world-views.[2] Something of this attitude is revealed in the statement that: "[W]omen in these situations are desperate for a solution and they are willing to take the chance that it may give them cancer".[3] The author does not say if he knows this for a fact or is just guessing, which is more probable in view of his endorsement of the distribution of: "unapproved medical products, if individuals autonomously choose to be engaged in the enterprise even though they may not be as knowledgeable as some opponents would like them to be".[4] If distributors of a drug are allowed to be incompletely informed, there is little room for recipients to reach enlightened decisions.

The acceptability of negative side effects in relation to purported benefits is not to be decided by benevolent paternalism; rather, it is for public health policies and for the affected population to evaluate, especially if the argument of lesser evil is invoked. Whether it is preferable to avoid pregnancy at the risk of getting cancer can only be decided by the women to whom quinacrine might be offered, supported by local health care officials who must assess the rationale of this approach as compared to alternatives.

Local health care policies are not a proper subject for heavy external criticism, for outside scholars are not immersed in the contextual cultural and economic forces at issue. Besides, less developed nations do have cadres of professionals, both in the medical and in the bioethical fields, who should be capable of assessing and counselling their own authorities in these matters.[5 6] And yet, Cooley goes quite a bit further by suggesting that countries which have rejected quinacrine should not have done so, nor should they ban "any other product that people choose to use". Under this premise, the Food and Drug Administration (FDA) and equivalent regulatory institutions must be declared superfluous, which is absurd, or a double ethics standard must be accepted whereby developed countries continue to enjoy pharmaceutical protection that in underdeveloped nations ought to be lifted. And that seems to be the conclusion Cooley reaches: "Even if it turned out to be the case that the buying and selling of unapproved medical products is unethical, it does not follow that we are obligated to put an end to it".[7] Since one can legitimately wonder if such a statement would ever apply in developed nations, it seems

that a double ethical fallacy is here being committed: to recommend policies of different moral probity, and to do so as a cultural outsider. In fact, Cooley's interventionism goes even further, for he explicitly disagrees with local authorities who for good moral reasons reject dubious medical practices.

RESEARCH STRATEGIES

At least four points of contention have been discussed concerning research protocols that developed countries have sponsored in the Third World: use of placebos, use of best existent treatments, equipoise, and informed consent.

Article 29 of the current World Medical Association's Declaration of Helsinki unmistakably condemns the use of placebos in control research groups, unless "no proven prophylactic, diagnostic or therapeutic method exists".[8] New medications can only be ethically compared with whatever is known to be the currently best therapeutic state of the art. Against such a clear statement, it has been argued that in countries with low or even non-existent standard therapies, "current placebo-controlled clinical trials ... are ethically justified".[9]

The suggestion that Helsinki should be read as addressing local therapeutic standards instead of widely accepted current treatments, has been vigorously challenged on the grounds that it creates a distinction between the ethics of research in poor and in affluent countries, since in the latter placebos are not allowed if adequate treatment exists. In a very enlightening review of pro and con arguments on this issue, Levine nevertheless states, in discussing the controversy over low-dose AZT regimen trials, that: "[T]his case is an example of a true ethical dilemma on which thoughtful and reasonable people can disagree".[10] The problem is that such a dilemma is only allowed to arise in Third World countries, for in affluent ones the use of placebos is banned if effective therapies exist, even though these countries do have poor populations for whom such therapies are de facto unavailable.

Arguments concerning placebos in the wake of existing effective therapy merge into those where substandard therapy is used in the possibly well meant effort to develop affordable alternatives to medication that is currently too expensive. The study may challenge best proven medication with some weaker alternative, or the trial may be designed to compare an abridged formula and placebo. In both cases, a number of patients will be subjected to a violation of Article 29 of the Declaration of Helsinki, which in its first part states that: "[T]he benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods". But, the counterargument goes, since trials are carried out in countries with precarious medical services, subjects "participating in these studies [where effective treatment is not employed] ... are not being *denied* treatment in the interest of science".[11] Again, we are confronted with a position which, if acceptable, ought to be equally valid for the poor population of affluent countries, which is definitely not the case.

Crusaders for the use of placebos and therapeutic short-cuts in clinical trials seem to forget that investigators enter a special ethical relationship with research subjects, especially if these are patients and, by bringing them close to effective treatment and then randomly excluding half of them, the investigators certainly deny these patients therapies that would be available were they not assigned to a control group or were the protocol designed in some other way. One may be exempted from moral responsibility if the needy can only be reached with difficulty, but it would be maleficent to deny such help to someone close by who can be easily assisted.

Most vexing are the numerous so-called natural history studies, where infection and transmission rates of diseases, notably HIV/AIDS, are observed by researchers who intentionally do not offer currently accepted treatment or preventive measures precisely because they wish to record uninfluenced biological processes, even if this means increased morbidity and mortality, a strategy sadly reminiscent of the Tuskegee Valley project.[12] In an unfortunately more cautious tone than employed in a previous editorial, Angell concludes that "all these questions are debatable, and that there may be few answers that apply to any situation".[13] This is a tolerant attitude that loses much of its appeal when considering that she is commenting on research done in Uganda under the sponsorship of a highly regarded First World university.

EQUIPOISE

The acceptance of research protocols employing placebo and weak therapeutic alternatives not only violates the spirit and the letter of the Declaration of Helsinki as well as the ethical standards required in developed countries, it also distorts the ethics of equipoise. "'Equipoise' is the point where we are equally poised in our beliefs between the benefits and disadvantages of a certain treatment modality, (or the preference of treatment A over treatment B)."[14] Consequently, randomised trials with control groups are only reasonable if there is clinical uncertainty, and all research subjects will be offered alternatives of which none is known to be worse, and where a more promising therapy is compared to the best available. In other words, equipoise ensures that no research subject receives either less than best proven treatment or the supposedly superior alternative being investigated. Careful attention to equipoise should discourage testing treatments that are less effective than currently available therapies. According to Brody,[15] equipoise occurs in clinical situations where the community of physicians has no reason or information to prefer one therapeutic alternative over the other but, more important, equipoise should bow to research when current treatments are challenged by an alternative that in some substantial way promises to be better—better because it is more effective, cheaper, less toxic, or has less unpleasant side effects. Otherwise, why research?

London agrees that local standards of availability, which he calls de facto local conditions, cannot set the standards of what would be circumstantial best treatment, or lack thereof.[16] Not only do circumstances vary, there also is no distinction between structural poverty, which is morally neutral, and imposed poverty through exploitation. Because de facto global standards, in the context of best existent therapy, generally do not obtain in Third World countries, London resorts to the local de jure standard "because this standard is built around the concept of clinical equipoise". Whereas de facto standards are based on what is actually feasible in a community, de jure standards, which can also be local or global, are more normative; global de jure standards contrasts the idea of "no known effective treatment for illness x anywhere in the world ..." with the more restricted construction which defines local de jure standards as valid for "no known effective treatment anywhere in the world for illness x within population p ..."[17]

Such a tour de force permits local research subjects to be exempted from any global de jure standard, with the excuse that what is widely known and accepted does not necessarily apply in the specific case under analysis. By this tenet, equipoise needs no longer apply to the comparison between an effective treatment and a promising alternative, but now adopts a rich but fuzzy view of therapeutic efficacy, so that not only biological but also cultural, in sum, a "wide range of [local] factors" are taken into account.[18] If enough local factors are considered, it should be easy to exempt the research team from applying generally accepted best therapies on the basis of the excuse that they have not been proven effective in this specific population under scrutiny. Thus, a local equipoise may be easily crafted, and be made to deviate from general, therefore scientifically supported, knowledge. A clinical equipoise situation can thus be envisioned by adapting a number of local factors. But if researchers can confidently feel they are

exempted from employing international standards of treatment, how do they design the proposed therapy? How do they exclude catastrophic side effects, if so little is supposedly known about the target population?

London wants his argument not only to allow disengagement from optimal treatment, but also to neutralise criticism that a placebo arm "would be denying subjects *care that has proven effective of their illness in their population*".[19] For these subjects had no access to such treatment anyhow because of their precarious de facto medical care. Such an argument would hardly be acceptable to ethics committees in a developed nation, which do not allow placebo controls when treatment exists, even though these treatments may be inaccessible to a substantial part of their own population.

Clinical equipoise would thus become a complex and adventitious concept instead of remaining an objective guideline to justify therapeutic research that is expected to yield improvements in medical management of disease. It may occur, of course, that local cultural or biological idiosyncrasies require a redefinition of what is elsewhere "standard", but such adaptations should lead to a stringently specified new standard, instead of infecting the idea of equipoise with the wide range of factors mentioned above. As equipoise is broadened but also becomes less determinate, the use of research placebos appears more acceptable, but the price is that the trial is increasingly disengaged from current knowledge, therefore unethical on account of being provincial and trivial. Again, such an altered formulation of equipoise has only been proposed for countries with low de facto medical standards, but would never be ethically acceptable in sponsoring nations, even for their uninsured population and for those others who cannot pay for adequate medical services.

POST-RESEARCH BENEFITS

Tailoring international research ethics to local insufficiencies in medical coverage brings up the question for whose benefit such trials are undertaken. Should they be of strictly local relevance? This would seem of little use to the sponsoring country. Perhaps the intention is to develop new markets or to altruistically benefit the poor, although this is doubtful when considering that drug companies increasingly rely on for-profit contract-research organisations (the so-called CROs). The fact is that in many instances "the clinical trial [of short course of AZT] conducted in Thailand will prove to be of little if any use to countries in the developing world".[20] In fact, local ethics committees are often confronted with post-marketing studies over lengthy periods of time, where subjects receive approved and efficacious medication for the duration of the study, with no provisos to assure availability of this medication for as long as clinically required after termination of the trial.

In a more recent article, Cooley[21] considers the Council for the International Organisation of Medical Sciences's (CIOMS) eighth guideline to be vague in its call for research benefits in host countries; he thus dismisses any requirement of distributive justice, ignoring Helsinki 2000 and its unmistakably clear demand for best proven and continuous post-trial treatment for research subjects. According to Glantz *et al*, CIOMS guidelines specify that: "... at the completion of successful testing, any product developed *will* be made reasonably available to inhabitants of the underdeveloped community on which the research was carried out..."[22] but the same source acknowledges that: "[T]he principle is often honoured in the breach, however". In fact, this is somewhat of a euphemism, for Helsinki stresses this point in unmistakably direct language: "At the conclusion of the study, every patient entered in the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study".[23] Unfortunately, such clearly stated ethical requirements have been denied by arguing that: "[N]either the assumption of special burdens nor the enhanced fiduciary responsibilities of researchers for their subjects can ground an entitlement to the best treatment available anywhere".[24] This is a blunt but unsupported disclaimer, which is invalid for research protocols applied in developed countries; it therefore goes clearly against the text and the spirit of Helsinki, and is also counterintuitive to what the ethics of research demand by, once more, tempting researchers to free themselves of commitments and responsibilities for the sole reason that they are operating in poor environements with precarious medical services. Research in Third World countries cannot therefore be redeemed as serving the interests of these host countries, for there is no guaranteed commitment beyond the research schedule, whereas the scientific benefits and marketable results go to the already properous sponsoring institution.

INFORMED CONSENT

Given the predicament that poor people are illiterate and lack deeper understanding of such concepts as autonomy, placebo, randomisation, side effects of medical treatment and other ideas that are part of any informed consent document in developed countries, researchers tend to simplify, or even avoid going into, appropriate details of information. Commenting on placebo-controlled HIV studies in Third World countries, Clark laments that: "due to the women's lack of knowledge and lack of true freedom, the interests of science and the "common good" are taking precedence over the well-being of the subjects".[25] Cooley's crusade for free quinacrine distribution, on the other hand, is based on the "duty to respect their [the recipients'] autonomous decisions regarding the use of non-approved medical products, even if they lack some information about the possible consequences of such use" because, he argues "[N]either the lack of information that some consumers may have to make their decision nor the unapproved nature of the product are sufficient conditions to make such actions unethical".[26] And his conclusion is that: "[T]he connection between the medical and business worlds should now be clear. In order to do what they ought, researchers and business people must legitimately believe that selling or giving the product to the Third World citizens will probably maximise utility", thereby assuring that "there is no real ethical dilemma about using drugs or any products that are banned in the developed world anywhere ... ."[27] Practices are once more defended for the Third World that would be inadmissible in developed countries.

CONCLUSIONS

Courageous and well argued papers have been published in defence of medical and research practices in Third World countries,[28 29] and many more have pondered the pros and cons of applying different ethical standards in sponsoring as opposed to host countries, often reaching lukewarm in-between conclusions. There is little doubt that research practices in less developed countries often short–cut ethical requirements that are respected at home. The aim of this paper is not to decry such practices, although such condemnation continues to be necessary, but to argue that there is an additional ethical fallacy commited by some First World scholars who continue to defend such divergent standards. Ethically dubious research practices will persist because, after sophisticated argumentation, most authors show considerable leniency and argue that local circumstances of poverty and lack of medical assistance justify some measure of ethical divergence. The present paper argues that double standards are not justified because developed nations will not tolerate them in their own poverty pockets. Willowbrook and Tuskegee are but two examples where local conditions in a developed country were finally not accepted as justifications for studies with ethically unacceptable practices.[30 31]

Many investigators and scholars are aware that the Declaration of Helsinki is adamant in requiring uniformly high moral standards for biomedical research.[32] Others,

nevertheless, have suggested that these standards "require clarification and perhaps modification",[33] and that placebos be accepted unless withholding current therapy entails the risk of death or disability. Further recommendations voiced by Levine include a modification of the Helsinki text from "best proven diagnostic and therapeutic method" to "best proven diagnostic, prophylactic or therapeutic method *that would otherwise be available to him or her"*(italics in original).[34]

There is a fair amount of anecdotal evidence that local research ethics committees have little power to influence or change protocols provided by sponsoring institutions from First World nations. Consent forms are rarely tailored to local cultural idiosyncrasies, researchers and host institutions are barred from information concerning coded side effects or about what is happening in other centres involved, and contracts clearly state that the sponsoring institution is the sole beneficiary of patent rights or royalties that might accrue. Host researchers are also excluded from any right to publish or otherwise make public the results of their work. Such practices are unfortunately bolstered by bioethicists who accept and foster double standards in research ethics. But there is something perverse in First World scholars publishing elegant essays that suggest reduced ethical standards for scientific and therapeutic medical practices in developing countries.

Should local ethicists, ethics committees or government policies decide to develop their own ethical standards, this will be unimpeachable and defendable under the banner of multiculturalism. Compromises are often made for material reasons, in order to gain funds and grant moneys, or foster exchange programmes. It is unfortunate that Third World countries should feel compelled to accept such financial support at the price of lowering their ethical standards, but this certainly is no reason to consider that sponsoring institutions should be supported in taking advantage of circumstances of need.

Commenting on Western condemnation of female genital surgery in some non-Western countries, Lane and Rubinstein suggest that: "[T]he further even a superb analysis is moved from the original investigatory question, the more damage is done by commiting the fallacy of detachable cultural descriptions".[35] This statement also applies to medical care, research practices, and the introduction of technoscientific developments. Drug trials and the marketing of pharmaceutical products are among the practices most often subject to scrutiny, but the conclusions reached are applicable to other situations where technological transfer occurs without heeding internationally accepted ethical standards. The addressing of issues surrounding the need for and the convenience of implementing local variations of ethical standards, and the opportunity to comment upon such issues, should remain a privilege of affected scholars, institutions, and governments. Analysts from developed countries would show an enhanced ethical sensitivity if they refrained from offering ethical deviations that are not allowed in their own countries.

REFERENCES

1 **Cooley D**. Good enough for the Third World. *Journal of Medicine and Philosophy* 2000;**25**:427–50.
2 **See reference 1:** 432.
3 **See reference 1:** 434.
4 **See reference 1:** 437.
5 **Freedman AM**. Chile bans quinacrine sterilizations in latest setback to U.S. distributors. *Wall Street Journal* 1998 Jul 10;sect A:4.
6 **Phantom sterilization—the quinacrine story**. http//www.africa2000.com/BNDX/BAO323.htm
7 **See reference 1:** 443.
8 **World Medical Association Declaration of Helsinki**. Edinburgh, 2000. http//www.wma.net/e/policy/17-c_e.html
9 **Levine RJ**. The 'best proven therapeutic method' standard in clinical trials in technologically developing countries. *The Journal of Clinical Ethics* 1998;**9**:167–72.
10 **Levine C**. Placebos and HIV lessons learned. *Hastings Center Report* 1998;**28**:43–8.
11 **Grady C**. Science in the service of healing. *Hastings Center Report* 1998;**28**:34–8.
12 **Caplan AL**. When evil intrudes. *Hastings Center Report* 1992;**22**:29–32.
13 **Angell M**. A letter to the editor [letter]. *New England Journal of Medicine* 1998;**338**:843.
14 **Johnson N**, Lilford RJ, Brazier W. At what level of collective equipoise does a clinical trial become ethical? *Journal of medical ethics* 1991;**17**:30–4.
15 **Brody BA**. *The ethics of biomedical research*. New York/Oxford: Oxford University Press, 1998.
16 **London AJ**. The ambiguity and the exigency: clarifying 'standard of care' arguments in international research. *Journal of Medicine and Philosophy* 2000;**25**:379–97.
17 **See reference** 16: 391.
18 **See reference** 16: 392.
19 **See reference** 16: 393.
20 **Crouch RA**, Arras JD. AZT trials and tribulations. *Hastings Center Report* 1998;**28**:26–34.
21 **Cooley DR**. Distributive justice and clinical trials in the Third World. *Theoretical Medicine and Bioethics* 2001;**22**:151–67.
22 **Glantz LH**, Annas GJ, Grodin MA, *et al*. Research in developing countries: taking 'benefit' seriously. *Hastings Center Report* 1998;**28**:328–42.
23 **See reference 8:** art 30
24 **See reference 20:** 29.
25 **Clark PA**. The ethics of placebo controlled trials for perinatal transmission of HIV in developing countries. *The Journal of Clinical Ethics* 1998;**9**:156–66 at 161.
26 **See reference 1:** 431, 437.
27 **See reference 1:** 444.
28 **Angell M**. The ethics of clinical research in the Third World. *New England Journal of Medicine* 1997;**37**:847–9.
29 **Lurie P**, Wolfe SM. Unethical trials of intervention to reduce perinatal transmission of the human immunodeficiency virus in developing countries. *New England Journal of Medicine* 1997;**337**:853–6.
30 **Jones JH**. The Tuskegee legacy. *Hastings Center Report* 1992;**22**:38–40.
31 **Rothman DJ**. Were Tuskegee & Willowbrook 'studies in nature'? *Hastings Center Report* 1982;**12**:5–7.
32 **Rothman DJ**. The shame of medical research. *The New York Review* 2000 Nov 30:6064.
33 **Bloom BR**. The highest attainable standard: ethical issues in AIDS vaccines. *Science* 1998;**279**:186–8. Quoted in reference 32:63.
34 **Levine RJ**. Quoted in reference 32:62.
35 **Lane SD**, Rubinstein RA. Judging the oher: responding to traditional female genital surgery. *Hastings Center Report* 196;**26**:31–40 at 37.