

MODULE FOUR: STANDARDS OF CARE AND CLINICAL TRIALS

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ABSTRACT

This module examines ethical debates about the level of care that should be provided to human research participants. Particular attention is placed on the question of what should be considered an ethically acceptable control arm. You will also learn what relevant international and domestic regulatory documents say about standards of care.

INTRODUCTION

Questions about the standards of care that should be guaranteed to participants in clinical trials have been among the most controversial issues of international research ethics during the past decade. High-profile and often heated debate has largely focused on the question of *what should count as an ethically acceptable control arm* in medical experiments involving human participants and (accordingly) the question of whether or not the clause of the *Declaration of Helsinki* that addresses this issue should be revised. Particular attention has focused on placebo controlled studies of (prophylactic therapy aimed at the prevention of) mother-to-child transmission of HIV that: 1) were sponsored by developed countries; 2) were hosted by developing countries; 3) would not have been permitted in the developed countries that sponsored them; 4) conflicted with the *Declaration of Helsinki* requirements; 5) purportedly aimed to benefit developing world populations; and 6) purportedly posed potential benefits but no real risks to human subject participants. This module reviews the history of these controversial trials and the debate that surrounded them.

HISTORY

Mother to child transmission of HIV

In 1994, medical research in wealthy developed countries demonstrated that treatment with zidovudine (AZT) reduced the risk of mother-to-child transmission of HIV to approximately one-third of what it would have been without treatment, from 25% to 8%. The trial protocol, known as ACTG 076, subsequently became the standard of care in wealthy developed countries for the prevention of HIV transmission from infected pregnant women to babies.¹ This method of intervention was expensive, however, costing approximately US \$800 per pregnancy, and thus unaffordable in impoverished developing countries (in sub-Saharan Africa in particular) where the burden of HIV was (and is) by far the most severe, and where governmental healthcare budgets are 'often less than \$10 per person per year.'² Given that 95% of HIV infected persons live(d) in developing nations, there was motivation to examine whether or not a shorter course of zidovudine, which would be less expensive and thus more affordable to poor populations, might also be effective in the reduction of HIV transmission from mother to offspring.

Additional experimentation was therefore pursued. Later in 1994, 'officials of the WHO, UNAIDS, the US NIH, and the US CDC designed placebo controlled studies' of a short-course treatment of zidovudine which would cost only \$80 per infected woman, with the aim to determine if this would be more effective than the *standard practice*, in developing countries, of doing nothing to prevent HIV infection of new-borns.³ While sponsored by wealthy developed nations, the trials were hosted in poor countries such as those they aimed to benefit: 'Côte d'Ivoire, Uganda, Tanzania, South Africa, Malawi, Thailand, Ethiopia, Burkina Faso, Zimbabwe, Kenya, and the Dominican Republic.'⁴

Criticism

Mainly because of the fact that the short-course study was tested against placebo rather than the ACTG 076 protocol, the studies

¹ U. Schüklenk. Protecting the Vulnerable: Testing Times for Clinical Research Ethics. *Social Science and Medicine* 2000; 51: 969–977.

² D.B. Resnik. Developing Drugs for the Developing World: An Economic, Legal, Moral, and Political Dilemma. *Developing World Bioethics* 2001; 1: 11–32.

³ Schüklenk, *op. cit.* note 1.

⁴ P. Lurie & S. Wolfe. Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries. *The New England Journal of Medicine* 1997; 337: 853–856.

in question sparked off heated international debate. Initial criticism was provided by Peter Lurie and Sidney Wolfe in a famous article in the *New England Journal of Medicine* in 1997. Among other things, critics claimed that the trials violated Declaration of Helsinki guidelines regarding standards of care for human research participants and the clause concerning ethically acceptable control arms in particular. The relevant article of the version of the Declaration of Helsinki current at the time explicitly stated that '[i]n any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method.'⁵

The purpose of this requirement is to protect potentially vulnerable research participants from being harmed by being deprived of standard medical treatment while participating in experimentation. The clause states that the safety and efficacy of a new form of treatment (or diagnostic method) for any given condition should be compared with the most effective proven treatment (or diagnostic method) for that condition, assuming that proven effective treatment exists. According to this requirement, placebo controls are unacceptable when proven efficacious treatment exists. The point is that sick patients who end up in control arms of experiments should not be left with no treatment whatsoever (expect for placebo) – or sub-optimal treatment – if more could be done to improve their conditions. A morally unacceptable scenario is one where a given individual would get no effective treatment for her disease if she does participate in a study, and ends up in a placebo control arm when, in fact, she would have received effective treatment – or perhaps a cure – if she did not participate. In this scenario the patient would be severely harmed as a result of involvement with the study. Whatever the motivation, this would be considered morally unacceptable if the *Declaration of Helsinki* requirement that '[i]n research on [human participants], the interest of science and society should never take precedence over considerations related to the well-being of the subject'⁶ is taken seriously.

The baseline of care that research participants should expect if they end up in control arms of studies, then, is the standard

⁵ *Declaration of Helsinki*. October 2000. 52nd World Medical Assembly. Edinburgh. Available at: <http://www.wma.net/e/policy/b3.htm>

⁶ *Declaration of Helsinki IV*. September 1989. 41st World Medical Assembly. Hong Kong. In *The Nazi doctors and the Nuremberg Code: Human Rights in Human Experimentation*. 1992. G.J. Annas & M.A. Grodin, eds. New York. Oxford University Press: 339–342.

of care for their particular condition; and, according to the equipoise requirement, those who end up in treatment arms should receive a treatment which might reasonably be expected to be as good as (or potentially better than) the current standard of care. Between 1) the clause of the *Declaration of Helsinki* in question, and 2) the equipoise requirement, then, reasonable protection of research participants is provided because neither those who end up in the treatment arms nor those who end up in control arms of studies are (with confidence) expected to receive care worse than they would have received if they had not participated in experimentation to begin with.

Standard of care requirements such as these motivated much (but only part) of the outrage which surrounded the infamous Tuskegee syphilis study which took place from 1932 until 1972 in Alabama (in the South of the USA). In this study, 400 rural black men were left untreated when diagnosed with syphilis – despite the fact that a penicillin cure became available ‘by the early 1950s’⁷ – so that the natural course of the disease could be observed. (Tuskegee researchers were additionally criticised for 1) being racist, 2) failing to obtain consent from participants or even inform them that they were being studied, and 3) intentionally misleading patients to believe that diagnostic visits would involve provision of ‘special treatments’ for their disease.⁸

In addition to pointing out that the placebo controlled mother-to-child transmission (MTCT) studies in question violated *Declaration of Helsinki* guidelines – which were, and largely still are, internationally accepted and considered *the* canonical requirements regarding research ethics – critics accused the trial sponsors and the ethics committees that approved the studies of employing *double standards*. This is because the same clinical trials would surely not have been approved to take place in the wealthy developed nations, such as the United States, that sponsored them. Precisely because the ACTG 076 protocol was available in the wealthy world, *placebo* controlled studies of a shorter course of treatment would not have been permitted there. Due to the fact that ethics committees in wealthy countries approved studies that would have been forbidden in their own countries to take place in poor countries, critics claimed that different standards of research ethics were being applied: one standard for rich countries and a different, weaker standard for impoverished countries. Given the primary

⁷ L.O. Gostin, ed. 2002. *Public Health Law and Ethics*. Los Angeles. University of California Press.

⁸ *Ibid.* Schüklenk, *op. cit.* note 1.

purpose of research ethics guidelines – to protect *vulnerable* persons – the application of weaker standards to *impoverished* populations in particular would be especially worrisome.

Defence

Defenders, however, argued that the use of placebo control in the MTCT studies posed potential benefits but no risks to subject participants. Given the standard practice in the developing world countries where the studies took place to provide *no treatment* for the prevention of vertical transmission of HIV, participants who ended up in the control arm were deprived of no treatment they otherwise would have received. If they had not enrolled in the trials, then *nothing* to prevent HIV transmission to their babies would have been provided anyway, given the existing economic and infrastructural constraints of local contexts. The benefits of study participation, on the other hand, included counselling. Those assigned to the treatment arm additionally received treatment likely to reduce the risk of HIV transmission to offspring. While those who ended up in the placebo arm nonetheless benefited from counselling, they were not harmed because they were not denied any effective treatment they would have received had they not participated in the study.

Since the studies in question posed potential benefits but no risks to participants in the contexts where the trials actually took place, defenders argued that studies like these are ethically acceptable. The point of research ethics requirements, they agreed, is to protect the vulnerable. In this case, however, the *Declaration of Helsinki* would be counterproductive in regard to the very people it aims to protect if it leads to the prohibition of studies that could benefit but, in any case, would not harm them. If the *Declaration of Helsinki* in fact forbids such studies, they argued, then the *Declaration of Helsinki* should be revised. From an individual standpoint these studies benefit participants by providing (counselling and) a decent chance of receiving a likely effective treatment they otherwise would not have received. From a societal standpoint, the studies aimed to benefit impoverished vulnerable populations through development of affordable prophylactic treatment. If the purpose of research ethics guidelines is to protect vulnerable individuals and populations, then they should not prohibit the very studies most likely to benefit such individuals and populations.

The solution, defenders of the studies argued, is revealed by recognising the purpose of the clause of the *Declaration of Helsinki*

we have been talking about. The point of that clause, they claimed, is that research participants in control arms should not be denied proven effective treatments they otherwise (i.e., if they had not enrolled) would receive. An ethically acceptable control arm, many concluded, is one where participants receive the *locally available standard of care* for their condition, because it is (only) denial of this that would in effect *harm* them if they end up in the control arm – because it is (only) denial of this that would *make them worse-off* than they would otherwise have been (i.e., if they had not enrolled in the study).

Scientific Issues

Part of the debate also revolved around scientific aspects of the studies. Defenders argued that comparing the short course of AZT with the ACTG 076 protocol would fail to address the scientific question that the trials aimed to answer. The purpose of the studies was to determine if the short course of AZT would be better than what was normally provided in local developing world contexts to prevent MTCT of HIV – i.e., nothing. Because knowledge of the *absolute effectiveness* of a short course of AZT was wanted, placebo control was claimed to be necessary. Comparing the short course of AZT with the ACTG 076 protocol would answer a different scientific question, providing information only about the *relative efficacy* of the short course. This might reveal how much worse (if at all) the short course would be than the ACTG 076 protocol for prevention of vertical HIV transmission in the populations in question; but, it would not clearly reveal how much better (if at all) the short course would be than doing nothing in the very same populations. Given relevant differences – with respect to things like infrastructure, nutrition, hygiene/sanitation, general levels of health and healthcare, etc. – between the populations where the ACTG 076 protocol was initially tested and the populations where the short course was later to be tested, there would be (it was argued) no straight-forward way to determine the absolute efficacy of the short course in the populations it was being developed for unless placebo controlled trials were conducted.⁹ Thus, sticking to a strict interpretation of *Declaration of Helsinki* requirements would have precluded scientific determination of the effectiveness of therapies aimed at

⁹ D.M. Studdert & T.A. Brennan. Clinical Trials in Developing Countries: Scientific and Ethical Issues. *The Medical Journal of Australia* 1998; 169: 545–548.

improving the health of the poor, according to defenders of the studies.

Critics, on the other hand, rebutted that placebo controls were unnecessary because *historical* controls would have sufficed. While we cannot address the scientific complexities of this debate in great detail here, it is important to point out that, despite the fact that historical controls can fail to meet the ideals of scientific methodology perfectly (because they can be prone to bias and because factors such as the expectations of investigators and participants, counselling, demographic changes, public education, and so on might account for any changes observed between those treated in a study and those observed historically), they are sometimes considered legitimate – especially when the effects of treatment appear to be dramatic.¹⁰ To this challenge, defenders argued that placebo controlled studies, in addition to maintaining the highest standards of scientific rigour, require smaller numbers of research participants and provide the fastest means of providing statistically significant results. In light of the urgency of the HIV/AIDS situation in the developing world, determining the effectiveness of new treatments sooner rather than later would result in saving a large numbers of lives.

Economic Issues

The more general claim (of defenders) that placebo controlled MTCT trials should be considered ethically acceptable in impoverished contexts where the standard of care for vertical transmission of HIV is no treatment, since participants who end up in control arms would not be harmed because they would not be deprived of any treatment they otherwise would have received in such contexts, was also challenged by critics. Udo Schüklenk, for example, argues that

This argument is hard to accept, because in the real world there is no such thing as a fixed local standard of care. Rather, the local standard of care in, for example, India, is a standard of care determined by the prices set by Western pharmaceutical multinationals. The only reason why the trials Lurie et al. criticised took place at all, is the pricing schedule set by the

¹⁰ ICH Harmonised Tripartite Guideline. 2000. *Choice of Control Group and Related Issues in Clinical Trials, E10*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Available at: <http://www.ich.org>

manufacturer of that drug. Glaxo-Wellcome therefore, more than anything else, determines what is described by some bioethicists and clinical researchers as the 'local standard of care' . . . If we take the local standard of care idea to its logical conclusion, it would be in the interest of Western companies to keep the prices sufficiently high to prevent many people from access to drugs, because this would legitimise further research on other drugs that could not otherwise take place.¹¹

Schüklenk's points, then, are 1) that the unavailability of drugs to the populations in question does not vindicate the use of placebo control when those ultimately backing the trials – i.e., profit-driven pharmaceutical companies – are themselves responsible for the unavailability of drugs, because of the unacceptably high prices they set to begin with, and 2) that weakening standards of care requirements could further promote conflicts of interest. A related, more general, point sometimes made (by Schüklenk and others) is that the answers to *ethical questions* should not be determined by *economic criteria*.¹²

Harm?

Another challenge to the 'no-harm' argument is that it fails to take account of psychological and social realities. In addition to worries about standards of care, the trials in question were criticised for flaws in the process of obtaining informed consent. One worry is that the agreement to study participation by community leaders – and complex social dynamics in hierarchical communities – may have put pressure on individuals such as disempowered females (whose consent was also, admittedly, sought) to participate. If truly autonomous individual decision-making was not part of the process, then this itself should be considered a harm – assuming that autonomy is an important (independent) component of life quality, as is argued by Dan Brock.¹³ It is also likely that – because of poor explanations, lack of education, language barriers, and the role ascribed to physicians – many participants never really understood that chances were good that they would be given a placebo and/or never really understood what 'placebo' means. (In related developing world trials, it was determined that only 25% of one group of women understood what a placebo

¹¹ Schüklenk, *op. cit.* note 1.

¹² F. Luna. Is 'Best Proven' a Useless Criterion? *Bioethics* 2001; 15: 273–288.

¹³ D. Brock. 1993. Quality of Life Measures in Health Care and Medical Ethics. In *Life and Death*. New York. Cambridge University Press.

was.¹⁴) Numerous participants presumably believed that they would inevitably receive effective medical interventions – believing that these are just the things that doctors provide – and this may have led to harm from false expectations, avoidable disappointment, and the failure to take other precautionary measures.

Benefit?

The ideas: 1) that the trials in question would benefit populations of the developing world countries where they took place; and 2) that producing results quickly was necessary in order to save many lives are also questionable. The fact remains that the prophylactic treatment for the prevention of vertical transmission of HIV remains routinely *unavailable* in most places where the MTCT studies occurred. Apparently no mechanisms were in place to assure that treatment would actually be made available to host populations when the trials proved treatment efficacy. South Africa is a case in point. Prophylactic treatment is only just now, long after the conclusion of controversial trials, becoming available in this country – and only as the outcome of a prolonged legal battle with the government. Florencia Luna argues that the ‘benefit of the relatively *immediate availability of the tested drug or therapy*’ is the weakest link of arguments in favour of ‘double-standards’ of care, citing numerous examples from ‘a long history that shows that in an important number of situations, availability did not occur.’¹⁵

POLICY

International guidelines

Declaration of Helsinki

In response to the controversy surrounding the MTCT trials in particular, an international debate questioned whether or not – and/or how – the World Medical Association’s *Declaration of Helsinki* should be amended to accommodate such studies. Critics of the MTCT trials argued, for reasons we have already examined, that strict requirements of a ‘universal standard’ of

¹⁴ G. Ramjee, N.S. Morar, M. Alary, L. Mukenge-Tshibaka, B. Vuylsteke, V. Ettiegne-Traore, V. Chandeying, S.A. Karim, L. Van Damme; COL 1492 study group. Challenges in the Conduct of Vaginal Microbicide Effectiveness Trials in the Developing World. *Aids* 2000; 14: 2553–2557.

¹⁵ Luna, *op. cit.* note 12.

care should be maintained, and that human research participants should accordingly be guaranteed access to the best treatments, available anywhere in the world, for their conditions. Defenders of the trials, on the other hand, argued that such strict restrictions would harm both vulnerable individuals (who would be deprived of participation in potentially beneficial studies) and vulnerable impoverished populations (which would be deprived of treatments developed through studies specially aimed at their benefit).

During the course of debate, several alternatives to the relevant clause of the *Declaration of Helsinki* were proposed. One proposal, in a draft document of the declaration circulated in March 1999, for example, was that the clause should read as follows:

In any biomedical research protocol every patient-subject, including those of any control group, if any, should be assured that he or she will not be denied access to the *best proven* diagnostic, prophylactic or therapeutic method *that would otherwise be available to him/her*.

This thus proposed that the provision of the *local standard of care* would suffice as an ethically acceptable control arm, implying that placebo control studies such as the MTCT HIV trials we have discussed should be permitted.

Another proposal, in a draft declaration circulated in May 2000, recommended that:

In any medical study, every patient – including those of any control group, if any – should be assured of *proven effective* prophylactic diagnostic and therapeutic methods.

According to this proposal, participants assigned to the control arm of a study should receive *some* proven effective treatment for the condition in question, assuming that proven effective treatment(s) exist. However this proposal says nothing about *how* effective a treatment participants (in control arms) should receive in scenarios where there is more than one proven effective treatment (and where some treatments are known to be more effective than others). This proposal was in one way stronger – but in another way weaker – than the 1999 proposal. It was stronger than the 1999 proposal because it would have required that control arm participants receive some effective treatment, assuming some proven effective treatment exists, even in contexts where the locally available standard of care for the condition in question is no treatment (whereas the 1999 draft would have permitted placebo control in such a situation). It was weaker than the 1999

proposal, on the other hand, because it would have apparently allowed control arm participants to receive proven treatments *less effective* than even the locally available standard of care – when the provision of relatively effective (though perhaps sub-optimal) proven treatment is standard practice in the community being studied. If there is more than one proven effective treatment for the condition in question, the May 2000 draft would require that control arm participants receive one of them; but, it does not specify that they should necessarily receive the *best locally available* treatment.

Both the March 1999 and May 2000 declaration drafts, of course, proposed weaker standard of care requirements than those specified by the version of the *Declaration of Helsinki* current at the time – i.e., that ‘[i]n any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method.’ In October 2000, the declaration was finally revised and, although the wording was slightly changed from ‘best proven’ to ‘best current’, the stricter standard of care requirement was apparently maintained. The adopted, and currently effective, version of the *Declaration of Helsinki* states in paragraph 29 that:

The benefits, risks, 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. (World Medical Association)

In 2002, however, a ‘Note of Clarification on Paragraph 29’ was added, stating:

The WMA [World Medical Association] hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that *in general* this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, *even if proven therapy is available*, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method;
- or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients

who receive placebo will not be subject to any additional risk of serious or irreversible harm.

According to this clarification, then, the MTCT studies might be considered ethically acceptable, under the latest version of the declaration, *if* the scientific justification (previously discussed) is in fact compelling. The strength of the arguments in support of the scientific necessity to use placebo control in those particular studies, in any case, remains debatable.

Additions:

Although the substance of clause 29 of the October 2000 *Declaration of Helsinki* did not involve great change from the previous version (perhaps until the above-mentioned footnote was added), other amendments, involving standards of care, served both to strengthen the protection of research participants and to promote the interests of communities where research takes place. Additional new clauses, for example, include the following:

Clause 19

Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

Clause 30

At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

Clause 19 addresses the kind of worry described by Luna: that research which purports to promote the interests of the communities where it takes place often fails, in fact, to do so. The addition of clause 19 explicitly requires that research should only be done on a particular population if the fruits of that research could realistically be expected to benefit that particular population. According to this requirement, it would be ethically unacceptable to test a new treatment, for example, on an impoverished population unless there is reason to believe that the treatment will be affordable and will actually become available to that population if the treatment is shown to be effective. Among other things, this may require verification that 1) there would be political willingness to make the treatment available in the local context and 2) the necessary infrastructure (to deliver the treatment) exists or is likely to be put in place. What exactly would constitute 'a reasonable likelihood' and the exact means by which such likelihood

should be verified are not specified by clause 19 as it stands. In any case, a clear implication of the clause is that it would be unethical to use members of an impoverished population as research participants in experiments aimed at the benefit of other – e.g., rich – populations (even when research participation poses no real harm to the research participants involved).

Clause 30 on the other hand addresses the standards of care that research participants should receive *after* the completion of experiments. If a new treatment is shown to be superior to the control arm therapy against which it is tested, for example, then all subject-patients should be guaranteed access to the new treatment afterwards (when appropriate from a clinical perspective). A motivation of this requirement is that all participants should stand to gain from their research participation and consequent contribution to the advancement of medical science. As with clause 19, the exact requirements of clause 30 are somewhat vague. Nothing is said, for example, about the duration of time that participants should be provided with treatment, following trial completion. In AIDS treatment studies, for example, should patients be guaranteed provision of HAART (highly active retroviral therapy) cocktails, or whatever comprehensive treatments may be shown to be superior, for the rest of their lives? Clause 30 likewise says nothing about who exactly – the research sponsors, the researchers, or local governments, for example – should ultimately be responsible for the provision of post-research medical care; nor does it say how it should be verified (before or after clinical trials take place) that this kind of requirement will be met.

It should also be noted that there are some kinds of trials for which clause 30, as it stands, would fail to provide any benefit to those who end up with sub-optimal therapy during study participation. Imagine those who end up in placebo control arms of experiments involving *preventative* therapies – such as HIV vaccine. When such individuals become infected with HIV during the course of the study, providing them with a vaccine proven (by the study) to be effective in the prevention of HIV would do them no good after the fact.

An open question, then, is the kind and extent of treatment, if any, that should be guaranteed to those who become ill during clinical trials aimed at the investigation of treatments or therapies other than those that the participants will actually need after the trials. Many have argued that HIV vaccine trials should not go forward unless research participants are guaranteed provision of comprehensive treatments for HIV/AIDS in the event that they do become infected during the course of clinical investigation.

Similar concerns apply to those who become infected during microbicide trials. Providing treatment to those who become ill during the course of preventative trials may be especially important when infection is at least partly a result of the fact that the preventative therapies under investigation fail to be effective.

Conflict:

Getting back to the issue of what is, or should be, considered an ethically acceptable control arm, it is important to recognise ways in which the world of international research guidelines has significantly changed in recent years. While numerous other international and local policy guideline documents regarding the ethical conduct of research involving human participants have existed for quite some time, the World Medical Association's *Declaration of Helsinki* was generally accepted as 'the gold standard' of guidelines that should be adhered to. While other documents added provisos, specifications, or additional requirements, they had also usually explicitly stated that consistency with the *Declaration of Helsinki* was expected. For better or worse, this is no longer the case. The current situation is one where various prominent research ethics guidelines appear to break away from Helsinki's demands. Different decisions about how to resolve the debate on which we have focused, thus, were made and embodied in alternative documents.

CIOMS/WHO

A 2002 document produced by the Council for International Organization of Medical Science (CIOMS) in conjunction with the World Health Organization (WHO), entitled *International Ethical Guidelines for Biomedical Research Involving Human Subjects*,¹⁶ for example, says the following about what should count as an ethically acceptable control arm:

¹⁶ Discrepancies are likewise found in international research ethics guidelines produced by the US National Bioethics Advisory Commission (NBAC) and the UK's Nuffield Council on Bioethics. US National Bioethics Advisory Commission. *Ethical and Policy Issues in International Research*. Available at: <http://www.georgetown.edu/research/nrcbl/nbac/clinical/Chap2.html>. Nuffield Council on Bioethics. *The Ethics of Research Related to Healthcare in Developing Countries*. Available at: <http://www.neufieldbioethics.org/publications/developingcountries/rep000000848.asp>

Guideline 11: Choice of control in clinical trials

As a general rule, research participants in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive *an established effective intervention*. In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo or ‘no treatment’¹⁷

The (mere) requirement that control arm participants receive ‘an established effective intervention’, of course contrasts with the current October 2000 *Declaration of Helsinki* requirement that control arm participants receive the ‘best current’ intervention. This CIOMS/WHO guideline is basically the same as the previously discussed May 2000 draft of the *Declaration of Helsinki*, which was ultimately rejected by the World Medical Association. In addition to posing weaker requirements than the *Declaration of Helsinki* in this way, the CIOMS/WHO guidelines allow an exception to the above rule:

Exceptional use of a comparator other than an established effective intervention. An exception to the general rule is applicable in some studies designed to develop a therapeutic, preventive or diagnostic intervention for use in a country or community in which an established effective intervention is not available and unlikely in the foreseeable future to become available, usually for economic or logistic reasons. The purpose of such a study is to make available to the population of the country or community an effective alternative to an established effective intervention that is locally unavailable . . . An argument for exceptional use of placebo control may be that a health authority in a country . . . seeks to develop an affordable intervention specifically for a health problem affecting its population. There may be then be less reason for concern that a placebo design is exploitative, and therefore unethical, as the health authority has responsibility for the population’s health, and there are valid health grounds for testing an apparently beneficial intervention.

It appears that this document was explicitly drafted to accommodate arguments like those put forward by defenders of the MTCT trials.

¹⁷ Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization (WHO). 2002. *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva. Available at: http://www.cioms.ch/frame_guidelines_nov_2002.htm

Local guidelines

Department of Health

Turning to the South African context, current law regarding standards of care for research involving human participants, although somewhat ambiguous, appears to likewise break with the *Declaration of Helsinki*, allowing that control arm participants receive the 'locally available' rather than necessarily the 'best' treatment for their condition. The Department of Health's *Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa* require the following:

1.2 B. Study Designs

The design of the drug trial should in no way prejudice the ongoing treatment and care of patients, nor should it in anyway undermine or confuse patients with respect to the best available local standard treatment practices and national policy approaches.

9.2.2 Research Standards

Vulnerable communities are often characterised by sub-optimal living conditions and poor access to health and social services. This should not lessen the need for high research and the use of universally accepted ethical standards. It is imperative that good research and ethical standards be applied to vulnerable and non-vulnerable communities.

9.3.2 Placebo Controlled Trials

Ethical guidelines that apply to controlled therapeutic trials are generally sufficient to protect the rights of HIV-infected persons. A special case involves the use of placebo after an intervention has been shown to be effective. The general principle is that the use of placebo in these circumstances is unethical. However with increasing disparities in health care between wealthy and poor countries, therapy that has been shown to be effective is often unaffordable in resource-poor settings. This is particularly true of therapeutic advances in HIV infection, which is a far bigger healthcare problem in poor countries in sub-Saharan Africa than it is in the industrialised countries. It may be justifiable to use placebo in communities that do not have access to interventions that are the standard care in resource-rich settings.

In order to reach the ethical principle outlined above, the balance between potential harms and benefits should be such

that the potential benefits to the community would considerably outweigh the harm. This issue is controversial and there is no international consensus. Widespread consultation is advisable prior to embarking on such studies.¹⁸

CONCLUSION

A concern about the status quo is the lack of harmonisation between various existing research ethics guidelines. In contrast to the past, where the Declaration of Helsinki was recognised as *the* authoritative document to which others must adhere, consensus about standards of care and the question of what should count as an ethically acceptable control arm in particular no longer exists. Those who criticised the MTCT studies and fought to maintain the strict standards initially embodied in the *Declaration of Helsinki* worry that those who wish to conduct ethically problematic research may now feel justified by appealing to other documents with weaker standards.

On the other hand, given the extent of controversy which has surrounded these issues, and given that many presumably well-intentioned and informed medical professionals, ethicists, and policy makers seriously believe – for the *prima facie* good reasons we have considered – that something less than the ‘best’ treatment for a disease can sometimes serve as an ethically acceptable control arm, some might say that it is appropriate that this issue has been resolved (or left unresolved) the way it has. Reaching any one answer to this inherently controversial issue and imposing it as *the* ethical requirement that must be adhered to everywhere in the world might look like ethical imperialism. If particular governments and individuals are informed and decide that they wish to, respectively, allow placebo controlled studies to take place within their borders or participate in them – because the studies in question, in the current situation, would likely benefit both those countries and individuals – then why should they be prevented? Why should any one idiosyncratic answer to an inherently controversial question gain global sovereignty?

A danger about leaving decisions in the hands of individual governments, local ethics committees, and/or individuals, on the other hand, is that vulnerable individuals might not then be protected after all. It is important to recognise that human rights

¹⁸ South African Department of Health. 2000. *Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa*. Available at: http://www.doh.gov.za/docs/policy/trials/trials_01.html

protection is weaker in some countries than others – and usually weakest in developing countries. Developing world policy makers will not always have the best interests of their citizens in mind and, furthermore, will not always be competent. It would be a shame if international ethical standards simply varied as a function of the good will and competence of local leaders.

To those opposed to paternalism, letting individuals decide for themselves what kinds of studies they want to participate in might sound like an alternative solution to the question of what should count as an ethically acceptable control arm. It must be remembered, however, that the ideal of informed consent, for numerous reasons, is difficult to perfectly achieve in developing countries. If this were not the case, then such a solution would be more promising. Given the potential for *exploitation* of those with severely restricted options, in any case, informed consent alone might still be inadequate.

FOR FURTHER THOUGHT

In your opinion, should the *Declaration of Helsinki* have been revised to weaken its requirements regarding standards of care for control arm participants? Why or why not? If you think that the arguments of those who criticised MTCT studies should prevail over the arguments of those who defended them, or vice versa, then explain why. Do you consider the current lack of consensus among research ethics guidelines on the question of what should be considered an ethically acceptable control arm to be a morally acceptable scenario? Should one particular answer to the control arm question be set as the standard for all international research? Explain.

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