BIOETHICS OUTLOOK

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Access to Health Care Through Research?

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In this issue

The Declaration of Helsinki is the single most important international document about the ethics of research conducted on human beings. First created after the Second World War, it has been revised on several occasions in the last fifty years. The most recent revision took place against a background of debate about the relationship between, on the one hand, enrolling people in clinical trials of new drugs and, and on the other, providing them with health care. For many poor people, in many poor parts of the world, the only way to access the kinds of health care that the rest of us take for granted is to participate in a clinical trial. In the first part of this issue, Mary Byrne discusses the ethical challenges, to researchers, pharmaceutical companies, non-government agencies and governments, of these new social circumstances. And we take the opportunity to publish the latest version of the Declaration in the second part of the issue.

During the 1990's clinical trials were undertaken in several African and Asian countries studying the use of a low dose of AZT to prevent maternal-foetal transmission of HIV in pregnant women. These trials caused considerable controversy. Two issues were significant, the use of a placebo treatment arm in the trial[1] and the fact that the treatment would not be available in some of the countries following the trial, even if evidence were to emerge that lower treatment reduced the rate of maternal-foetal transmission.[2]

The use of a placebo arm was controversial because a standard of treatment existed in the developed world. This standard, however, involving high doses of AZT over longer periods of time, was not available in the countries where the low dose was trialed; the standard of care in these countries was no treatment. Hence the argument supporting trials utilising a placebo was the fact that it was being compared with the 'local' standard of treatment. Undertaking the trial in places where it was known in advance that the local government would be unable to fund and provide even a low dose regime of AZT, were

it to be demonstrated to be beneficial, was controversial as the participants and their community would bear the risks of the trial with little or no access to the future benefits. Any benefits would accrue to wealthier nations, and to the company financing the trial.

Before this trial there had been a seachange in the ethics of research in regard to participation in research and access to the newly validated treatments. A significant factor in this changing understanding of research ethics, particularly clinical trials, was the response to early experimental therapies for AIDS at the time when there was no recognised treatment for the deadly disease. While the new drugs were being tested in clinical trials, there was a strong demand by persons with AIDS and their advocates to allow experimental therapies outside of the trial. One slogan of the time was "A Drug Trial is Health Care Too".[3] This move, in fact, led to greatly increased funds for larger trials in the United States of America.[4]

Similar questions of access are now arising in research involving new treatments for people with cancer and with chronic medical conditions. There is a greater awareness in affected communities of research being undertaken. Through the media and the Internet, patients and their families now have access to information about clinical trials for experimental therapies and are asking to join such trials. Some projects consequently have more applicants than places for participants. In addition, medications and other forms of therapy are becoming increasingly costly to develop and provide while governments, health insurance companies and other funders of health care, working with limited resources, are becoming more selective about what will be funded. It is in this research and health care climate that the Declaration of Helsinki was revised.

In the remainder of this paper I will provide a description of the revisions of the Declaration and then argue that health care and research are different. Research cannot be perceived as a substitute form of health care. However, participants in research trials may make a claim on the researchers for ongoing access to newly validated therapies in light of the relationship that has developed and their acceptance of the risks of the research trial.

Changes to the Declaration of Helsinki

The Declaration of Helsinki is a statement of the World Medical Association. It was established in 1964 and has been reviewed five times since then. The fifth revision was approved at a meeting of the World Medical Association in October 2000.[5] While the Declaration was initially proposed for medical practitioners, it is now recognised as one of the major international statements of the ethical principles of medical research.

This fifth review produced a substantially revised Declaration. There are three major sets of changes. Firstly the revision strengthens the emphasis on the priority of the well-being of research participants over the interests of science and society. Hence the primary duty of the researchers is to protect research participants (*Declaration 2000*, paragraph 10) mainly by minimising risk in the design of the research and by rigorously assessing all possible risks and any claimed potential benefits prior to undertaking the research (*Declaration 2000*, paragraphs 16-18).

Secondly, it emphasises openness and public accountability. The Declaration now requires that members of the public be able to access information on the design of particular research studies (*Declaration 2000*, paragraph 16) and sources of funding for specific projects (*Declaration 2000*, paragraph 22). The Declaration also stresses the importance of publishing both positive and negative results (*Declaration 2000*, paragraph 27).

Thirdly, greater ethical guidance is provided relative to the locations of research and the

groups of people who can be approached as potential participants (*Declaration 2000*, paragraphs 19, 29-30). These sections are crafted to ensure that such participants and their communities will have ongoing access to the beneficial outcomes of research. While the impetus for this third group of changes has been the consideration of research undertaken in developing countries by researchers from developed countries, these revisions are also significant in developed countries as healthcare systems change and people struggle to access expensive new medical treatments.[6]

Access to health care through research

The slogan mentioned earlier, "A drug trial is health care too" describes a particular view that sees clinical trials (research activities that involve medications and other healthcare therapies) as a kind of health care. Such statements deepen the confusion participants may have over the difference between research participation and clinical care. Where the researcher is both researcher and treating physician, and the participant is both participant and patient, the boundaries of research and clinical care can become blurred.

The argument supporting such a view is that new therapies being trialled in clinical research offer at least the potential for benefit. Therefore people who wish to access that benefit, and who are willing to accept the potential risks, should not be denied such access. This argument is strongly presented in the cases of people suffering from serious or "terminal" illness for which there is no validated or accepted beneficial treatment. Consequently, it could be argued, trials need to be enlarged or people need to be allowed to access very promising experimental therapies before the trials are concluded and before the drugs or therapies are approved by regulating bodies.[7] This stance marks a shift from focussing on the risks of research participation, and therefore the protection of participants, to the benefits that may accrue from participating. In fact it has been demonstrated that participating in research, even if only receiving standard treatment rather than the experimental treatment, can be of benefit for the participant.[8]

But there is still a powerful argument against the equating of research and health care. Research has a different purpose from health care: The aim of research is to obtain generalisable knowledge. The aim of health care is to use existing knowledge to help an existing patient. The primary focus of the researcher is a null hypothesis, valid research design and rigorous research technique. The primary focus of patient care is to identify and pursue the best interests of the patient. These may be conflicting goals.[9]

There are additional reasons for not equating research with health care. Increasing the number of participants in research beyond those needed for statistically valid results may well delay reaching conclusory end points. Allowing access to experimental therapies outside of research in an effort to maximise access to potential benefit (quasi access to health care) could overturn the rigour of the science needed to demonstrate the efficacy of the new therapy as the use of the therapy would not be monitored at the same level. It would also be very hard to withdraw the new therapy from the community if it turned out to be less efficacious than first predicted. Then the community as a whole and future people in need of health care would suffer. This is not a promotion of the interests of science and society over the well being of the participants. The understanding of 'well-being' is based more in minimising risk rather than maximising potential benefit.

The arguments described above have some merit, but the argument against allowing research to be an alternative form of access to health care is stronger. This is not to deny the fact that some participants will gain therapeutic benefit from participating in clinical trials and may well be motivated to enter such trials in the hope of gaining access to therapeutic benefit. Rather, the responsibility of researchers is research rather than providing access to health care. Supporting this position will mean that some people will miss out on the benefits of new treatments until they have been validated. The appropriate response to this problem is to ensure that the methods by which people gain access to research trials, and the potential benefits of such trials, are just and equitable, rather than to attempt to make researchers responsible for providing access to increasing numbers of eager potential participants.

Access to health care after research

The editor of the *Bulletin of Medical Ethics* described paragraph 30, a new paragraph, as "the most far-reaching of all the changes" in the Declaration.[10] The main focus of this section is to prevent research being undertaken in developing countries where it is cheaper to do the research but in circumstances in which the researchers have no intention of ensuring ongoing access to beneficial treatment following the conclusion of the research project. Such research is gross exploitation.

As well as the above, however, there are many other less obvious situations where the research participants may not be able to access the new therapies identified and validated in the research following the conclusion of the trial. New therapies tend to be expensive and many governments and other health care funders opt not to pay for, or at least not substantially to subsidise, such therapies. In addition there may be a gap of several years between the conclusion of the trial and final regulatory approval of the therapy which would enable regular access. Consequently the person who had access to the therapy in the research trial may not be able financially or legally to access the effective treatment.

Again there are two perspectives on this problem. On the one hand it could be argued that the participants, as partners in the research who bore the risks of the research project, are entitled to some ongoing benefit, particularly if they did not receive the beneficial therapy during the trial and the experimental therapy is successful. Furthermore, it can be described as unethical to offer a person access to a new medical therapy that offers greater benefit than current standard therapy for a set amount of time and then to withdraw access to that therapy once the research project is completed. That is cruel. Although the goal of research is knowledge, care and concern for the participants is also essential.

On the other hand it could be argued, as has been argued above, that research should not be equated with health care. Then, researchers do not have an ongoing responsibility to the participants of a research project, particularly if the participants have been clearly told the limits of the project. For health care, in general, participants are a part of the general community and their ongoing needs are properly the responsibility of the participants themselves and the respective providers and funders of health care in that community. Furthermore, strictly interpreting and enforcing the requirement of Paragraph 30 may have a detrimental impact on the costs of some trials or the size of trials, decreasing the number of places in research projects. Alternatively, expensive therapies that a person may need access to for many years may not be developed or research may

be restricted to places where this requirement is not requested or enforced.

Again, both positions have some merit. Research participants have given something by participating in a research project, and to that extent have some claim to benefit. However, researchers do not take on total responsibility for ensuring that research subjects have access to ongoing health care. However, it can be argued that part of a research design should incorporate ongoing access for research participants to therapies that have been found to be beneficial to them. The basis for this is that priority must be given to the welfare of the participants and concern for their welfare does not end at the end of the trial. This is explicitly supported by the Declaration of Helsinki with paragraph 30. There would be some justifiable situations where this requirement may not hold, such as early safety trials where there is not enough evidence to demonstrate a benefit or when the trial has been inconclusive. However, the presumption should be on ongoing access unless it can be strongly argued against.

Implications

I have argued that research should not be conflated with health care, and that it should not be perceived as an alternative means of access to health care. Such ideas would be detrimental both to research and to health care. The underlying issue in the debates described above relates to the funding and provision of health care. The changes to the Declaration of Helsinki respond not only to certain recent and strongly debated research practices, but also to the inequities in the provision of, and access to, decent health care in different parts of the world. By seeking to find ways to make reasonable health care accessible to more people under the umbrella of research, the revisions of the Declaration have blurred the boundaries of responsibilities for researchers.

Responsibility for the provision of health care, and therefore for the maintenance of healthcare structures varies according to the local and country context. In any place it is complex and varied but properly lies with communities, individuals and governments. Research impacts on the provision of health care, through the provision of information confirming the effectiveness of current treatments and the development of new treatments. The benefits of research are broader than the immediate therapeutic benefits for participants and for others who will gain access to the new therapies. Researchers must also consider the probable availability of, and reasonable access to, newly developed treatments in the context of the local community. Choosing research priorities should not happen in isolation from the local community and local healthcare planners.[11] In paragraph 19 the Declaration has highlighted this responsibility of researchers.

However, the Declaration does not clearly identify the responsibility that lies elsewhere in relation to the provision of health care, and so has blurred the boundaries of responsibility of researchers in its attempt to address access to health care issues. 'Participants' need to be clearly understood as those who are already, or who specifically will be, enrolled in research projects, so that claims by anyone who wishes to access the potential benefits can be answered. Further amplification of paragraphs 19 and 30 is needed in order to clarify the scope of responsibility for ensuring ongoing benefit for the population and the appropriate arenas of responsibility for the provision of health care.

Having access to decent and beneficial health care is something that would be wished for all people. It is obvious that a large proportion of the world's population do not have this. It is also the case that some people currently suffer from conditions for which there is no truly beneficial therapy. Neither of

these problems will be resolved by the current Declaration of Helsinki, and it is important that researchers focus on the second issue. Then their contribution to the first issue will be as concerned members of the wider global community seeking to support, with their expert knowledge, developing ways of providing decent health care for everyone.

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References

1 To use a placebo treatment arm means not to provide an active treatment to a proportion of the research participants. Either a group of the participants will receive no treatment or they will be given a "dummy" treatment, something that resembles the active treatment but has no active ingredients. A placebo treatment group is generally used in research when no standard beneficial treatment exists for the condition being studied. The argument for using a placebo group is that research participants may improve simply because they are participating in research and may believe they are receiving the experimental therapy. Comparing results from the group on the placebo with results from the group on the active treatment enables the researcher to identify which results are attributable to the active treatment under study.

2 Macklin, R., "After Helsinki: Unresolved Issues in International Research" *Kennedy Institute of Ethics Journal* 11(1) pp. 24-25.

3 Moreno, J.D. "Goodbye to all that: The End of Moderate Protectionism in Human Subjects Research" *The Hastings Center Report* 31(3) p. 15.

4 Mastroianni, A. and Kahn, J. "Swinging on the Pendulum: Shifting Views of Justice in Human Subjects Research" *The Hastings Center Report* 31(3) p. 26.

5 The revised version is reprinted in this edition of *Bioethics Outlook.*

6 Moreno, pp. 9-17; Mastroianni and Kahn pp. 21-28.

7 Such a perspective, particularly access outside of research trials, is developed more strongly by Udo Schuklenk in his *Access to Experimental Drugs in Terminal Illness: Ethical Issues* Pharmaceutical Products Press: Binghamton, NY, 1998.

8 Bastian, H., "Gains and Losses For Rights of Consumer and Research Participants" *BMJ* 323(7326) pp. 1419-1421.

9 Shorr, A.F., "AIDS and the FDA: An Ethical Case for Limiting Patient Access to New Medical Therapies" *IRB: A Review of Human Subjects Research* 14(4) p.4.

10 Official Statements, *Bulletin of Medical Ethics* 162 (October 2000) p. 11.

11 Grady, C. "Science in the Service of Healing" *Hastings Center Report* 28(6) p. 36.

Declaration of Helsinki (2000)

World Medical Association

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended at Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996, and Edinburgh, October 2000.

A. Introduction

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

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9. Research investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. Basic principles for all medical research

10. It is the duty of the physician in medical research to protect life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

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.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

C. Additional principles for medical research combined with medical care

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

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

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.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

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