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Post-trial obligations

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Abstract
In its essence, post-trial obligations describe a duty by research sponsors to provide a successfully tested drug to research participants who took part in the relevant clinical trials after the trial has been concluded. In some instances, this duty is extended beyond the research participants. This article is divided into three main parts. The first part outlines the legal basis for post-trial obligations by looking at international guidelines, including those issued by the World Medical Association. National legislation is exemplified through resolutions and guidelines issued by Brazil and South Africa respectively. The second part analyses the ethical foundation for post-trial obligations, in particular the attempt to minimize exploitation of research subjects. The third part raises obstacles and challenges for the implementation of post-trial obligations. The jury is still out on whether post-trial obligations in the form of access to drugs for clinical trial participants is the best, or even a good way, to avoid exploitation in medical research.

Keywords
*i*nternational research ethics; post-trial obligations; bioethics; exploitation; international justice

Introduction

In its essence, post-trial obligations describe a duty by research sponsors to provide a successfully tested drug to research participants who took part in the relevant clinical trials *after* the trial has been concluded. In some instances, this duty is extended beyond the research participants.

Every year, more than one and a half million people die of tuberculosis (World Health Organization 2007). Most deaths occur in developing countries and many could be avoided if treatment times were shorter (Hope for... 2007). In July 2007, the St. George's Medical School in London started a four-year trial to speed up treatments, which take six months (Hope for... 2007). Many patients, particularly in developing countries, stop taking their medication halfway through the course because of the distance to their treatment centre or because they begin to feel better. Those proposing the trial assume that a four months treatment period would allow more patients to conclude their course and thereby save lives. The shortened course started the testes on 1,200 patients in Mozambique, Zambia, Zimbabwe, and South Africa in July 2007.

This trial will be taken as a guide and reality check for the analysis of post-trial obligations. Assume that one of the 1,200 trial participants is an invented figure, called

Mr. Mokolele, from Zimbabwe. Mr. Mokolele lives in a rural part of Zimbabwe and has no guaranteed access to health care. Also, assume that Mr. Mokolele develops tuberculosis again two years after the completion of the trial – like any bacterial infection, tuberculosis can re-occur, that is, it can be caught and cured more than once. And, finally, assume that the trial was successful. The efficacy and safety of the shorter course of tuberculosis was established.

What now? What are Mr. Mokolele's rights to or chances for post-trial access to the new tuberculosis treatment? Some topics in research ethics have been discussed for more than a generation; for instance, the requirement to obtain informed consent from individual research subjects. Other topics have not. Post-trial obligations are one of the new topics, which explains the considerable uncertainty surrounding it.

This article does not deal with post-trial obligations, which are taken for granted today, namely the right of accidentally injured research subjects to treatment and compensation. It is uncontroversial that research subjects should receive free medical treatment and/or compensation for accidental injury through interventions performed solely for the purposes of research. Ethics committees are usually expected to review details of plans, including insurance coverage, for research-related disability or even death.

This article outlines the recent stances on what should be offered to research participants after a trial is concluded. It analyses the opinions of several international and national regulations. Also, it addresses the ethical foundation for potential post-trial obligations, and eventually presents the obstacles and challenges of this new topic.

For the purposes of this article, the term "developing country" will be used to describe countries where a considerable part of the population (more than one third) does not have access to the successful products of medical research (Macklin 2004).

International guidelines

International guidelines are rarely legally binding. They are usually statements issued to guide the practice of certain professions. Whether guidelines have the power to achieve compliance or not is often dependant on their support from a certain profession.

In 2003, the International Society for Archaeological Prospection was founded (2007). The aim of this society is to promote high standards of research in the field of archaeology. Suppose that archaeologists and geophysicists working in this area sometimes encounter situations they find difficult to handle. Their understanding of scientific research might, for instance, break certain taboos of indigenous populations, such as the search for skeletal remains using ground-penetrating radar. When the members meet in their new society, they discuss these topics and notice that they apply across countries. After a while, the members agree to set up a committee that formulates guidelines for such cases. The purpose of the guidelines is to help researchers in their daily work. Whether these guidelines are powerful in terms of compliance does not depend on the law. If there were national or international laws governing the acts under question, for example, searching for skeleton remains, decisions would not be difficult to make. There would only be a choice between compliance or illegality. But when there is no legal enforcement mechanism, guidelines derive their main power from the organizations that formulated them. If the entire profession of archaeological prospection is represented through the above named society and if there is general agreement that guidelines are needed, the chances of compliance are high.

Taking this argument into account, only one international guideline has real power today - the Declaration of Helsinki, by the World Medical Association.

World Medical Association
Declaration of Helsinki

In 1926, doctors from several countries formed the *Association Professionnelle Internationale des Médecins*, an organization aimed at discussing problems of practising medicine across borders. The organization suspended operations during World War II after achieving a membership of 23 countries. During the war, the meeting house of the British Medical Association became the new focal point for doctors who wanted to compare medical practice in different countries. Two conferences held in London initiated plans to form a new organization, which was going to be called "The World Medical Association (WMA)". In 1947, the First General Assembly of the WMA was held in Paris with founder members from 27 countries.

Shortly after its inauguration, the WMA started to receive requests for guidelines on how physicians ought to treat human subjects involved in research. The horrors of Nazi experiments on humans, revealed through the Nuremberg Trials, made the need for drawing up such guidelines pressing. After a decade of discussions, the WMA issued a draft Declaration, which was adopted by the 18th General Assembly in Helsinki, Finland, in 1965. Changes to the declaration were made in 1975, 1983, 1989, 1996, and 2000.

Today, the WMA represents over eight million physicians from 84 countries (World Medical Association 2003). Of those organizations currently involved in the formulation of guidelines, the WMA has the most reasonable claim to be taken seriously (Schüklenk 2004). Consequently, the Declaration of Helsinki can be regarded as the most important international document in research ethics.

It was only in 2000, at the 52nd WMA General Assembly in Edinburgh, Scotland, that post-trial obligations made an entrance in the Declaration of Helsinki. Since then, Article 30 reads: "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" (World Medical Association 2004).

Article 30 is one of only two, which is supplemented by a note of clarification. In 2004, at the General Assembly in Tokyo, Japan, the WMA requested that post-trial access to drugs, medical procedures or care be discussed during the *planning* of trials and documented in the study protocol.

The document is very clear. If a research subject takes part in a clinical trial, he or she should expect post-trial access to successfully tested drugs or procedures. In addition, the organisers of the clinical trial should include how they will manage post-trial access in their study protocol. In this regard, the declaration makes a substantial and a procedural demand. Post-trial access must be provided (substance) and documented in the study protocol (procedure). In other words, researchers must be clear on how to provide post-trial access before the study begins.

What does article 30 of the Declaration of Helsinki mean for the 1,200 research subjects from Mozambique, Zambia, Zimbabwe, and South Africa? Or more specifically what does the article mean for hypothetical Mr. Mokolele, who contracted tuberculosis two years after the study was concluded?

First, Mr. Mokolele should receive access to the shorter course tuberculosis treatment according to article 30 of the declaration. Second, the study sponsors should have described post-trial access arrangements in their protocol. Hence, theoretically at least it should be possible for Mr. Mokolele or his family to find out how to access the tuberculosis drug.

It is necessary to remember, though, that post-trial obligations were first mentioned in the Declaration of Helsinki in 2000 and that the requirement for outlining access mechanisms in the study protocol was only added in 2004. Given that non-compliance with the declaration has no legal consequences, unless enforceable international or national laws prescribe the same conduct, one cannot expect full conformity with immediate effect. However, given that the Declaration of Helsinki represents more than eight million physicians world-wide, the chances are high that awareness of post-trial obligations and genuine attempts at compliance should increase significantly in the very near future.

Council for International Organizations of Medical Science
International Ethical Guidelines for Biomedical Research Involving Human Subjects

The Council for International Organizations of Medical Science (CIOMS) was established jointly by the World Health Organization (WHO) and the United Nations Educational, Scientific and Cultural Organization (Unesco) in 1949. It is an international, non-governmental organization, which works on a non-profit basis. Their International Ethical Guidelines for Biomedical Research Involving Human Subjects is one of the most frequently quoted research ethics guidelines in academic literature.

The current version (2002) supersedes the 1993 text and consists of general ethics principles and 21 guidelines. The text was designed to assist in the definition of national research ethics policies, with particular emphasis on developing countries. In contrast to the Declaration of Helsinki, CIOMS guidelines include a very helpful and extensive commentary.

Two guidelines are immediately relevant in the context of post-trial obligations: guidelines 10 and 21. Guideline 10 demands that: "Any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community" (CIOMS 2002).

The term "reasonable availability" is contested. What does it mean to make a product reasonably available to a population? CIOMS do not answer this question. Instead they note that the decision has to be made on a case-by-case basis. Relevant points to consider are: the length of time for which the study drug will be made available to research subjects or the local community; the severity of a research subject's medical condition; the effect of withdrawing the study drug; and the question of undue inducement if an intervention is provided free of charge. In this regard, their clarification focuses on post-trial access granted to research participants – for instance, asking to consider participants' medical condition –, whereas their guideline is broader and demands post-trial access for a population or community.

Overall, CIOMS notes that it is unethical to conduct research in a population that is unlikely to have reasonable access to the developed drug on completion of the study. Hence, if researchers cannot show that a product will be reasonably available to the research participants and the broader local community, they should not conduct the research in the locality. Guideline 21 notes that research sponsors are ethically obliged to ensure the availability of "services that are a necessary part of the commitment of a sponsor to make a beneficial intervention or product developed as a result of the research reasonably available to the population or community concerned" (CIOMS 2002).

Importantly, in the commentary to this guideline, CIOMS note that details of any post-trial obligations must be included in the consent process and document.

The two CIOMS guidelines mirror the two relevant Declaration of Helsinki guidelines. However, the CIOMS demands are stronger. The first refers to the substance of post-trial obligations, namely that a defined group should have access to the studied drug after the conclusion of the trial. The second refers to the process of how this post-trial access is documented.

On both counts, CIOMS is more demanding than the Declaration of Helsinki. Whilst the declaration notes that post-trial access is a benefit for research subjects only, the CIOMS guidelines expand this group to include the broader community or population. On the second topic, the declaration notes that post-trial access arrangements need to be documented in the study protocol, whilst CIOMS demands that they are incorporated in the consent form.

What difference would it make for Mr. Mokolele if the study he took part in complied with the CIOMS guidelines? Mr. Mokolele would already know how post-trial access to the tuberculosis drug would be provided to him. He would have read the details in the consent form, or it would have been explained to him verbally. At the same time, the drug would be available not only to him, but also to a wider population. The exact specification of beneficiaries beyond research participants is not provided by CIOMS, but it is probably fair to assume that his immediate family members, who live in the same household, would qualify. Given the highly contagious nature of tuberculosis, this is likely to be an important aspect of post-trial access for Mr. Mokolele.

World Health Organization
Operational Guidelines for Ethics Committees that Review Biomedical Research

The World Health Organization, founded in 1948, is the United Nations' agency which deals with health related issues. WHO's prime goal is to help citizens from around the world attain the highest possible standard of health. The organization is governed by 193 member states. It is therefore one of the very few organizations with representations from countries worldwide - 193 is the number of countries currently recognised by the United States State's Department. Alas, WHO has not issued any comprehensive international research ethics guidelines. Otherwise, the guidelines would be very powerful given WHO's world authority on health-related matters and its truly representative nature. However, in 2000, WHO has issued Operational Guidelines for Ethics Committees that Review Biomedical Research.

The objective of these guidelines is to ensure high-quality and consistent ethical review of biomedical research around the world. Meant to complement existing national laws, the guidelines should form the basis for detailed written procedures of ethics committees. In particular, they should be used to develop standard operating procedures.

The main task of an ethics committee lies in the review of research proposals with particular attention to the informed consent process and the feasibility of the protocol. Under the section *Elements of the Review*, the WHO document lists:"a description of the availability and affordability of any successful study product to the concerned communities following the research" (World Health Organization 2000).

Given the authority of WHO, this note to post-trial access is important. But how much can we draw from this sentence, the only one relevant to post-trial obligations in the entire document? The WHO document does not demand post-trial access to drugs, as the previous two documents do. This paragraph is included as a *potential* element of ethics review, not a compulsory one. However, two points are noticeable. First, "concerned communities" is more likely to fall in line with the CIOMS guidelines in their demand to open post-trial access beyond research participants. Otherwise, the wording would have been "concerned research participants" or similar. Second, if documentation of post-trial access is meant to be reviewed by ethics committees, it has to be available prior to the start of the study. On this count, WHOs agree with both the Declaration of Helsinki and the CIOMS Guidelines.

Does the WHO document help Mr. Mokolele? Not really. Even though post-trial access is mentioned in the WHO document, it is not mentioned as a compulsory element of ethical research and hence no firm policy position is taken.

Unaids
Ethical Considerations in HIV Preventive Vaccine Research

In 2001, government representatives from 189 countries attended the first-ever UN General Assembly session on HIV/Aids. Unanimously, they adopted the Declaration of Commitment on HIV/Aids, which acknowledges that the Aids pandemic presents a global emergency and a formidable challenge to human life and dignity. Part of the declaration refers to prevention of the disease, including prevention through vaccines.

One year earlier, in 2000, Unaids, a joint UN programme, which brings together individual organizations (for example, Unesco, Unicef), issued guidance on HIV vaccine research. This guidance is one of the strongest international demands for post-trial access to drugs (vaccines) yet.

Under guidance point 2, Unaids notes about vaccine availability: "Any HIV preventive vaccine demonstrated to be safe and effective […] should be made available as soon as possible to all participants in the trials in which it was tested, as well as to other populations at high risk of HIV infection" (Unaids 2000).

At the same time, Unaids asks research sponsors and researchers to plan ahead for post-trial access by discussing it at the initial stages of HIV vaccine development. In the same year, Unaids clearly underlines the substantive and procedural points made through the Declaration of Helsinki. Successfully tested drugs must be made available to the study population and the mechanisms for doing so must be discussed prior to the start of any research. Like the CIOMS guidelines, the Unaids document also sees post-trial access as applying to a wider group than those who took part in the research. In fact, in their explanatory notes they demand that attention must be given to how a vaccine could be distributed within the country in which it was tested, or even beyond. In this regard, Unaids goes further than CIOMS by talking of countries rather than communities as beneficiaries.

This last international guideline presented in this article is not directly relevant to Mr. Mokolele, as it only refers to HIV vaccines.

The four most prominent international research ethics guidelines agree on two points. First, post-trial access to drugs is a prerequisite for ethical research in the 21st century. Second, the mechanism for access needs to

be discussed and decided upon *before* the study begins. Smaller differences are present as to the beneficiaries of post-trial access ranging from research participants only, to local communities and populations to the entire country where the research was carried out. Demands on the documentation for post-trial access range from availability to ethics committees via the study protocol to availability to individual research participants via the consent form.

International guidelines do not have legal force. If Mr. Mokolele finds that he is not given post-trial access to the relevant tuberculosis drug, he might exude pressure by mobilising the media, but he cannot go to court. However, there are international laws which give citizens the right to pursue any grievances through the courts. Research ethics has made its way into one major such law, namely the International Covenant on Civil and Political Rights.

International covenant on civil and political rights

The International Covenant on Civil and Political Rights (ICCPR) entered into force in 1976 and has since been ratified by 152 countries (Office of the High Commissioner for Human Rights 2004). This means that almost 80% of the world's countries promised to adhere to its rules. In contrast to the Declaration of Helsinki or any other of the guidelines listed, the covenant is legally binding. This means that those who fully ratified it need to make sure that any provisions can be enforced through their own legal system.

Article 7 of the ICCPR specifies that: "[n]o one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation" (Office of the High Commissioner for Human Rights 2004).

This is all the ICCPR specifies on research ethics. The emphasis is clearly on obtaining informed consent from human subjects prior to their involvement in any research. Post-trial access to drugs is not mentioned, neither are other corner stones of research ethics, such as confidentiality or privacy. Still, it is worth noting that legally binding documents exist on an international basis, which include elements of research ethics. In the future, it might be possible to expand the ICCPR to acknowledge the fact that research ethics has moved forward in recent years.

National laws and guidelines

In terms of international guidelines, two main demands were made for post-trial access. First, that it should be provided in the first place (a substantive demand), and second that details of provision should be clear before the start of any research study (procedural demand). Some countries have moved one step further and incorporated such demands into legally binding legislation.

Brazilian National Health Council

In 1996, the Brazilian National Health Council (NHC) issued a resolution (No.196/1996), which emphasised the importance of the substantial demands. Research undertaken on Brazilian subjects must result in benefits for them. In particular, Article III.3 (p) demands that any research involving human subjects is required to: "ensure the research subjects the benefits resulting from the research project, in terms of social return, access to procedures, products or research". (National Health Council 1996).

Through this resolution, the Brazilian government imposes an affirmative obligation to provide post-trial access to drugs or procedures. On whom the obligation was imposed by this resolution was unclear, but clarified later.

In a more general statement, the resolution demands that communities should benefit from research after it has been concluded. However, this demand is less strict as it is prefaced by "whenever possible".

Interestingly, the Brazilian resolution makes no specific demands on the procedural side. In section IV (Freely Given and Informed Consent) it is outlined that research subjects should be informed of any risks, discomfort or benefits that might be expected. Although one could argue that the term *benefits* includes post-trial benefits, this has not been made explicit. And an explanation of potential benefits (e.g. of a therapeutic or diagnostic nature) is always part of an informed consent process. In addition, the resolution demands that research subjects are informed about any possibilities for medical follow up and/or care. Yet again, this is not explicitly linked to post-trial access of successful medical interventions, given that some trials include both medical follow up or care as part of the experiment.

One year later, the NHC issued a supplementary resolution (No.251/1997) which focuses on new pharmaceutical products, medicines, vaccines and diagnostic tests. In this resolution, post-trial obligations are confirmed further and it is clarified who should carry the obligation. Article IV.1(m) specifies that: "Access to the medicine being tested must be assured by the sponsor or by the institution, researcher, or promoter, if there is no sponsor, in the event its superiority to the conventional treatment is proven" (National Health Council 1997).

This means that Brazilian legislation is clear. Research sponsors or other specified groups have an obligation to provide access to drugs, which were tested on research subjects in Brazil – assuming, of course, that the results of the trials confirmed their safety and efficacy. This access needs to be provided at least to the research participants. The more general demand of "social returns" in the 1996 resolution might indicate that access should be provided beyond this group.

South African Medical Research Council
Guidelines on Ethics for Medical Research

In 2000, the South African Medical Research Council (SA-MRC) published their revised Guidelines

on Ethics for Medical Research, which are not legally binding. The earlier SA-MRC guidelines published in 1993 made specific reference to the procedural demand in post-trial access. Although no post-trial obligations were imposed on research sponsors or others, it was noted that participants have to be informed about the *potential* continued supply of drugs after the conclusion of a study (National Bioethics Advisory Commission 2001). In fact, the guidelines explicitly noted that participants do not have a right to post-trial access, unless special arrangements were put in place at the time of the trial. In this regard, the 1993 guidelines differ strongly from the Brazilian equivalent, which is very clear in its demand for post-trial access, but less clear about the procedural demand of how ethics committees or research participants ought to be made aware of post-trial access.

However, the new 2000 guidelines by the SA-MRC are less specific than the 1993 original. Post-trial access or obligations by sponsors to *individual participants* are not referred to explicitly. Under section 11, International Collaborative Research, two very general statements are made. First, as a benefit to the host country research must be translated into accessible care (South African Medical Research Council 2000). Second, the host country must benefit beyond pure financial gain, for instance, through community access to successfully tested drugs (South African Medical Research Council 2000).

In this regard, the South African guidelines have opted for a very general tone on post-trial obligations on both substance and procedure.

Brazilian National Health Council resolution is very clear on one point. Sponsors or their equivalents have a definite obligation to provide post-trial access to successful drugs at least to the research participants. However, it is unclear how ethics committees and/or research participants will be informed about the mechanisms of post-trial access. In contrast, the South African Medical Research Council has moved away from clear and specific substantial or procedural demands since 2000, leaving only general comments that can be interpreted to refer to post-trial obligations.

As for Mr. Mokolele, when one looks at guidelines, all seems well for him, or does it? Although several high-profile international and national guidelines demand post-trial access to interventions for research subjects, the demand has come under serious attack.

Ethical foundations for post-trial obligations

Why have post-trial obligations suddenly emerged as a serious demand in research ethics? Clinical trials have been conducted for decades and only in the 21st century has there been a strong call for obligations beyond the immediate trial. Two reasons will be outlined here, one regarding the avoidance of exploitation and one regarding the trust developed in researcher-participant relationships.

Minimizing exploitation

The sense of having been exploited can generate more resentment and mistrust than most other feelings (Emanuel et al. 2004). This is particularly so in the health care setting where one group is often already disadvantaged or vulnerable through a disease and the other group potentially holds the power to cure.

What exactly is exploitation and could it be avoided through post-trial access to medical interventions? Exploitation can be defined as the act of taking unfair advantage of another party to serve one's own interests (Wertheimer 1999; Macklin 2004).

In this context, it has been argued that testing medical interventions on impoverished populations who will not have access to results is exploitative (Annas & Grodin 1998). This is so because researchers who do not make the results of their trials available to research participants are exposing the poor and ill educated to risks in order to benefit more affluent populations (Crouch & Arras 1998). In this sense, they are taking advantage of one population to serve another.

How can taking unfair advantage be avoided? By rewarding those involved in a transaction appropriately for their contribution (Nagel 1991). But why have demands for post-trial access not been made earlier?

The reason is straightforward. In industrialized countries, where most pharmaceutical research used to take place, a viable and essentially fair exchange model is already in existence between the health care industry and human research subjects. Those who contribute to research are rewarded with direct benefits in the form of potentially therapeutic treatments and accessible new health care products and services in the future. Taking a wider perspective, they also receive indirect benefits in the form of jobs and affluence generated by a high-tech industry. The existence of this exchange model explains why the issue of post-trial obligations does not normally arise in the context of health care research (Participants in the... 2004; Schroeder & Lasen-Diaz 2006).

However, one main issue has thrown doubt on the fairness of this reward model: the potential for exploitation of research subjects in developing countries. In developing countries, one cannot take the above mentioned rewards or benefits for granted. On the contrary, reasonable availability of newly developed products cannot be guaranteed, neither can a match to the population's health needs nor the existence of secondary benefits, such as jobs.

A Canadian researcher working in Kenya said in an interview about awareness raising of HIV risks:

> We had a 16-year-old girl involved in our clinic and somebody tried to talk to her about HIV. She's the sole support for three or four younger siblings. You tell her she might get HIV, which might mean she'll get AIDS in ten years. Well, that threat doesn't seem real. Hunger is real. (Dunn 1997).

And, of course, if hunger and malnutrition are a problem, so is – usually – access to essential medicines,

particularly those that are still under patent protection. In those instances, the exchange model between the health care industry and researchers, which is taken for granted in industrialised countries, is ineffective. And this is where the demand for post-trial obligations fits in. In order to avoid exploitation of research subjects in developing countries, measures have to be put in place before research subjects around the world benefit from rewards that are already taken for granted in the West. And one such measure is to insist on post-trial obligations, in particular if sponsors and researchers come from affluent countries.

The topic of exploitation will be analysed from Mr. Mokolele's perspective. As current economic disparities mean that he cannot expect the range of standard benefits associated with taking part in research trials in the West, he must be compensated in some other way for taking risks and inconveniences. If not, researchers could be accused of exploiting him. And post-trial obligations are one way to redress this balance and to avoid the claim of exploitation. Hence, on grounds of avoiding or minimizing exploitation, Mr. Mokolele can expect access to the tuberculosis drug he needs two years after the completion of his trial.

Researcher-participant relationship

The promotion and safe-guarding of the health of the patients are considered the prime duty of a physician. The relationship between patient and physician is meant to be undisturbed by external factors. This is not the case in the relationship between research participant and researcher. Researchers have potentially competing obligations to sponsors or the aspiration to achieve progress in medicine. However, in both relationships trust plays a major role and the relations are often highly personal.

The break or end of a relationship between researcher and research participant can be very difficult, even traumatic, particularly for the participant. If – as is regularly the case in developing world settings – participation in a clinical trial is the only way to access clinical care, the end of a trial spells the end of health care.

Researchers working with Aids research subjects often find it difficult to stand by inactively in anticipation of their participants' death from a treatable disease (Shapiro & Benatar 2005). Needless to say that it creates an even stronger sense of loss for the research participant after the end of a trial, when this was the only way to access health care.

In some ways, the strongest form of loss arises for subjects in control groups of clinical trials. Their health is likely to have deteriorated further during the trial even if the intervention was effective and safe. On the other hand, research subjects enrolled in the treatment arm of an effective intervention already know that their health could be improved further, but this possibility is closed to them with the closure of the trial.

It is in this context that post-trial obligations to research subjects are being advocated. Focus group research conducted amongst patients, clinical researchers and administrators in Kenya showed that all stakeholders in research believe strongly that researchers have a long-term obligation towards participants. One of the participants is quoted as follows: "I have been used like a guinea pig, so how does he just leave me without compensation?" (Shaffer et al. 2006).

The participants accepted a risk for the advancement of knowledge, and in return they expect a benefit. This reason, given by the interviewed stakeholders, aligns with our argument for non-exploitation. Importantly, though, a number of participants in the focus groups noted that stopping potentially lifesaving therapy would result in a loss of trust between research participants and researchers, potentially leading to community's unwillingness to participate in clinical trials.

The trust and human interaction built through a research relationship provides a second argument for post-trial obligations. To abandon research participants who are in dire need of medical attention after a trial is considered unfair by both sides. Based on this premise, one could conclude that the greater the health needs of the participants and the clearer the health benefits of the tested medical intervention, the stronger the obligation to provide post-trial access (National Bioethics Advisory Commission 2001).

What would this mean for Mr. Mokolele? Tuberculosis is a deadly disease. Assuming that the trial in which he will take part is successful, obligations to provide another course of the drug are very strong.

Research subjects take risks and accept inconveniences to promote the advance of medical knowledge. They deserve benefits in return for their contribution. If they cannot receive the benefits that are taken for granted in some parts of the world, such as easy access to developed drugs, which are focused on local health needs, other compensatory solutions have to be found. Post-trial access to drugs is one of them. Without the provision of such benefits, research subjects would be exploited. Such compensatory measures also help maintain the trust that usually develops between research subjects and researchers.

For now, all seems well for Mr. Mokolele. Several high-profile international and national guidelines demand post-trial access to interventions for research subjects, and persuasive ethical foundations for such measures exist.

Obstacles and challenges

The four main arguments that have been brought forward against post-trial obligations will be dealt with followingly.

Time frame constraints

A serious practical obstacle for post-trial drug access for research participants is the long time frame of pharmaceutical research. Mr. Mokelele is taking part in a tuberculosis drug trial. The typical development time for a new tuberculosis treatment is 15 years (Hope for…

2007). After pre-clinical studies in the laboratory usually involving test tube studies and animal experiments, trials have to go through three stages. Simplified, Phase I clinical trials are conducted on a small group (20-80) of healthy volunteers to assess the safety and tolerability of a new treatment. The main question to be answered is: is the treatment safe or is it too toxic? Phase II clinical trials are performed on larger groups (30-300) of patients in order to test the efficacy of the treatment. Hence, the question to be answered is: is it working? Phase III clinical trials are carried out on yet larger groups of patients (300-3,000) in order to provide definitive information on the efficacy of a new treatment. Often, two separate Phase III clinical trials are conducted before regulatory authorities will grant marketing approval.

Mr. Mokolele is enlisted in a Phase III clinical trial, in which researchers are testing the new combination of existing antibiotics. This means that part of the usual 15-year time frame has already been reduced. The most serious time difficulties are those faced by participants in phase I and II trials. At the same time, marketing approval for these existing drugs was already available. This way, the sponsors of Mr. Mokolele's trial hope to reduce the development time from 15 years to five years. Two years after the trial will be concluded, the drug combination could technically be on the market and therefore available to him when he suffers again from tuberculosis. However, his is an unusual case. Given the more likely development period of 15 years for a new tuberculosis treatment, Mr. Mokolele's new infection would have come years before the drug could possibly have been marketed.

This time problem will be particularly pronounced for research participants in phase I and II clinical trials. But even those involved in phase III clinical trials may not receive access to post-trial drugs when they need them if not enough time has passed. And if post-trial access is restricted to the medical intervention under development, there is no solution to this problem.

Undue inducement

Much of the ethics of clinical trials rests on the legitimacy of the consent given by its participants. Research subjects have a right to self-determination and only their voluntary and knowledgeable agreement to undergo an intervention can legitimise their participation.

The information side of *informed* consent requires the explanation of a medical intervention's purpose, its potential benefits and foreseeable risks, as well as its alternatives – all in a way that is intelligible to a volunteer (Brody 2001). The *consent* aspect requires a non-coercive setting to obtain agreement as well as some form of authorisation or documentation. If a payment in money or kind has the potential to persuade a research subject to take excessive risks or volunteer against their better judgement, this situation is called undue inducement (CIOMS 2002). In communities with little or no access to health care, almost any payment or any medical care, however experimental, might constitute undue inducement.

In this regard, communities exist in which it will be almost impossible for researchers to avoid undue inducement (Kerns 1997). In such communities, post-trial access to drugs would add another and quite considerable potential inducement to an already imbalanced decision-making process (Participants in the… 2004).

Undue inducement is a serious obstacle to ethical research, and it is forbidden by all major international and national research ethics guidelines. However, this does not mean that undue inducement should be used as an argument to defeat efforts to achieve fair compensation for research subjects. Although the line between unethical inducement and appropriate compensation may be a fine one, it should not stop those responsible from designing appropriate mechanisms, especially where research participants in developing countries are concerned.

One solution to overcome the undue inducement obstacle is to exclude post-trial access information from the consent process. Instead, it should only be included in the study protocol for appraisal by an independent ethics committee (National Bioethics Advosiry Committee 2001). This suggestion would favour the procedural principles as outlined in the Declaration of Helsinki. And it would contradict the relevant CIOMS guidelines on information disclosure to potential participants. It has to be noted, though, that research participants can normally expect full disclosure of relevant facts in the informed consent process, and expected benefits are an essential part of the information.

Unrealistic demands

Two criticisms have been raised in the context of post-trial obligations that can be summarised as unrealistic demands. First, it has been argued that researchers are not responsible for remedying the problems of a country's health care system (Emanuel et al. 2004). In fact, it is unreasonable to expect researchers to find solutions for problems of global economy (Ashcroft 2002). Second, it was noted that imposing post-trial obligations on research sponsors could mean that valuable developing country research will not be undertaken due to prohibitive costs (Brody 2002).

At this point in time, it is not possible to predict whether post-trial obligations will lead to a reduction of useful trials in developing countries. However, South African bioethicist Solomon Benatar would say the following: "Requiring greater sensitivity to the plight of the poor and some degree of solidarity with them is not an excessive moral requirement" (Shapiro & Benatar 2005).

Minimizing exploitation requires flexibility

The main ethical argument in favour of post-trial obligations is the minimization or avoidance of exploitation. Only when benefits from a transaction are distributed fairly in line with contributions, can exploitation be averted. However, at the practical level this poses a considerable problem. Consider two different research participants: Jorge and Maria (Mr. Mokolele is not suited

to make this point). Jorge took part in a trial, which exposed him to significant risk, for instance, an early trial to test the efficacy of a new HIV vaccine. By contrast, Maria took part in a low-risk trial to confirm, for instance, the efficacy of a new intervention against mouth ulcers. Consider further the large profits the sponsor of Jorge's trial might achieve, if the HIV vaccine proved effective and safe in comparison to the profits the sponsor of the mouth ulcer trial can expect. And consider lastly the possibility that the latter sponsor could have built up a more comprehensive local health infrastructure to conduct trials in comparison to the former.

If the avoidance of exploitation requires a weighing of burdens and benefits, the above two cases should fare very differently. Post-trial access to successful drugs on its own might be inadequate if the risks taken by research participants and the potential profits for sponsors are both very high. By contrast, for very low or no-risk research for which other benefits are obtained at population level, post-trial access to the tested intervention might be excessive or unfair. Imposing a very specific benefit on an interaction between researcher and participant ignores other benefits of trials, which might be sufficient to avoid exploitation. These could be the training of health care personnel, the construction of a health care facility or the provision of public health measures (Participants in the… 2004).

One more complication to the above example involving Jorge and Maria will be added. What if Jorge's trial was unsuccessful? This would mean that no successful drug or procedure was developed. Jorge took significant risks for no benefit at all, not even benefits during the trial when he was given a drug that was either unsafe or not effective. In this instance, post-trial access to successful drugs as a means to avoid exploitation failed.

Overall one could argue the prescriptiveness of post-trial access to the successfully tested intervention is too rigid to successfully minimize exploitation.

The main practical obstacle to the usefulness of post-trial access to research participants is the long time span of pharmaceutical research. By the time a drug enters the market with full approval, it might be too late for many research participants to access this particular drug, the only one post-trial access gives them a right to. One also needs to consider the potential for undue inducement if post-trial access to successful drugs is promised to research participants. Those with no or little access to health care are already under pressure to enter trials, however experimental. Adding another considerable benefit could worsen the chances of researchers for receiving legitimate, genuine consent. It has also been argued that post-trial obligations would make trials in developing countries prohibitively expensive and therefore reduce their numbers by default. In a similar vein, it has been argued that post-trial obligations may be addressed at resolving issues of global economy, which is not the task of individual researchers or sponsors. And the last argument against rigid and prescriptive post-trial obligations links back to ethical foundation for such obligations. Namely, exploitation can best be avoided by flexible obligations judged on a case-by-case basis and taking risks and benefits into account. By insisting on a very specific set of duties (access to successful drugs post-trial), the chances of avoiding exploitation are not significantly reduced, if at all.

Conclusion

Research subjects take risks and accept inconveniences to promote the advance of medicine. In order to avoid exploitation and to foster a good relationship between researchers and participants, they deserve benefits in return for their contribution. Therefore, to provide successfully tested drugs to those who helped test them is one way of avoiding exploitation.

Post-trial obligations are a new topic in international research ethics. The relevant international guidelines only started to mention it in the 21st century. The Declaration of Helsinki demands post-trial access to drugs for research subjects and a clarification of provisions in the study protocol. The International Ethical Guidelines for Biomedical Research Involving Human Subjects developed by CIOMS are similar, but they name the broader community as a potential beneficiary of the successfully tested drugs, hence widening the obligation. At the same time, they demand that provisions are outlined in the consent forms and not only in the study protocol. Both guidelines are non-binding. However, national law in Brazil requires sponsors or their equivalents to provide post-trial access to successful drugs at least to the research participants.

Post-trial obligations are a contentious topic with both principled and practical objections ranging from the long time spans of pharmaceutical research, to undue inducement, to making trials potentially prohibitively expensive. The most damaging concern is that exploitation can best be avoided by flexible obligations judged on a case-by-case basis and taking risks and profits into account.

The jury is still out on whether post-trial obligations in the form of access to drugs is the best, or even a good way, to avoid exploitation in research. Although Brazilian legislation is clearer on these issues than many other, questions that are not finally resolved are: to whom should interventions be made available? To participants, to local communities, or to the whole country? And who is responsible for making such interventions available? Sponsors, researchers, researchers' institutions or even non-government organizations or Western governments?

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