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Research with vulnerable human beings

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ABSTRACT

Some categories of human beings are particularly vulnerable vis-à-vis medical research. Vulnerability could be considered as the liability to be harmed, exploited, deceived, cheated, wronged, or otherwise unfairly treated, in roughly that descending order of importance. Vulnerable human beings obviously include the incompetent (minors and mentally handicapped adults), the desperately poor, ill or ignorant, prisoners, refugees, pregnant women, subordinates in highly authoritarian systems, etc. Vulnerability in itself does not imply that no research whatsoever should be carried out with such categories of humans but only that it should be carried out only under very special conditions. In this paper I treat of vulnerability in research of particularly developing world populations; of the types of research which exploit such vulnerability, and of why and how research subjects should be protected. The aim in this paper is to stimulate practical reflection on the possible vulnerabilities of potential research subjects that researchers or investigators need to avoid exploiting rather than on an adequate theoretical treatment of the issue.

1. What some regulations state regarding vulnerability

In the first paragraph of the commentary on Guideline 13 of the CIOMS International Guidelines for Biomedical Research Involving Human Beings (CIOMS, 2002), vulnerability is defined as follows: "Vulnerable persons are those who are relatively (or absolutely) incapable of protecting their own interests. . .they may have insufficient power, intelligence, education, resources, strength or other needed attributes to protect their own interests." Although this definition could be criticized for being too objective, as making reference to "those others", it does pick out the main attributes which render human beings vulnerable.

The Declaration of Helsinki (WMA, 2008), the leading international regulatory document on research with human beings, addresses vulnerability in six of its articles: 9, 17, 26, 27, 28 and 29. It is worth carefully reading through all of these articles as each focuses on a different aspect of vulnerability. A general problem is that the document does not define "population" or "community", both of which are ambiguous, as referring to either persons sharing a common trait or attribute or persons inhabiting a common physical space. But the terms can be understood wherever they occur in either or both senses of the ambiguity without any problem.

Declaration of Helsinki article 9 states that

"Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence."

Declaration of Helsinki article 17 states that

"Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research."

Declaration of Helsinki article 26 states that

"When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship"

Declaration of Helsinki article 27 states that

"For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population repre-

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sented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden."

Declaration of Helsinki article 28 states that

"When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected."

Declaration of Helsinki article 29 states that

"Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative."

The CIOMS International Guidelines (CIOMS, 2002) treat of vulnerability in Guideline 13 and of two categories of particularly vulnerable humans in Guidelines 14 and 15. In these Guidelines the CIOMS spells out in clearer detail, using easily remembered bullet points, what is already clearly implied in the Declaration of Helsinki regarding vulnerable research subjects.

CIOMS Guideline 13: research involving vulnerable persons

"Special justification is required for inviting vulnerable individuals to serve as research subjects and, if they are selected, the means of protecting their rights and welfare must be strictly applied."

CIOMS Guideline 14: research involving children

"Before undertaking research involving children, the investigator must ensure that:

- the research might not equally well be carried out with adults;
- the purpose of the research is to obtain knowledge relevant to the health needs of children;
- a parent or legal representative of each child has given permission;
- the agreement (assent) of each child has been obtained to the extent of the child's capabilities; and,
- a child's refusal to participate or continue in the research will be respected."

CIOMS Guideline 15: research involving individuals who by reason of mental or behavioural disorders are not capable of giving adequately informed consent

"Before undertaking research involving individuals who by reason of mental or behavioural disorders are not capable of giving adequately informed consent, the investigator must ensure that:

- such persons will not be subjects of research that might equally well be carried out on persons whose capacity to give adequately informed consent is not impaired;
- the purpose of the research is to obtain knowledge relevant to the particular health needs of persons with mental or behavioural disorders;
- the consent of each subject has been obtained to the extent of that person's capabilities, and a prospective subject's refusal to participate in research is always respected, unless, in exceptional circumstances, there is no reasonable medical alternative and local law permits overriding the objection; and
- in cases where prospective subjects lack capacity to consent, permission is obtained from a responsible family member or a legally authorized representative in accordance with applicable law."

2. Triple vulnerability and rationalizations for research

Developing world populations, particularly those of Sub-Saharan Africa, are vulnerable in many dimensions as far as medical research is concerned. They are vulnerable as members of economically disadvantaged groups; a fact recognized in Helsinki #8 and CIOMS Guidelines 10 and 13. They are also vulnerable as members of medically disadvantaged groups, bearing a heavy burden of neglected or so-called orphan diseases. Then again, many of them are vulnerable as incompetent minors increasingly used as research subjects. In Sub-Saharan Africa, vulnerability is not limited to research subjects but extends to scientists, researchers, institutions, and even governments because of their relative lack of capacity and empowerment vis-à-vis their developed world counterparts.

In spite of these multiple vulnerabilities there has been not a decrease but an enormous increase in developed world medical research on human beings in the developing world, particularly in Sub-Saharan Africa. Although I have no handy statistical figures to prove this claim, personal anecdotal evidence abounds. During the past decade or so I have been a member of several ethics review committees, two in Sub-Saharan Africa and three abroad at the WHO and EDCTP. I have directly observed the increase in the number of research protocols before these various committees, the vast majority of them sited in Sub-Saharan Africa. Over the same period, I have equally been involved in capacity training in research ethics in Africa through teaching programmes such as those of AMANET, IRENSA, and SARETI. Anecdotal evidence from participants in these programmes, mostly research scientists and members of ethics review committees, clearly indicates continuing increase in the number of research projects and studies, spanning all disease specializations, in Sub-Saharan Africa.

This increase in research activity has been accompanied sometimes by convincing justifications and at other times by what are at best only rationalizations. Some of these are the following: it is argued that since the majority of diseases and epidemics, requiring research for solution, are occurring in the developing world, it makes sense to conduct the researches where the solutions are needed. It is also argued that the current researches are likely to result in medicines which are more available and affordable to developing world populations than currently existing ones. Furthermore it is pointed out that the process of researching will contribute to capacity-building and infrastructure development in the developing world. It is even argued that the availability of epidemics and abundant sundry diseases and lack of constraining regulatory frameworks can be considered as incentives for market-driven research which otherwise would not be attracted to invest resources into such research.

All this indicates that developing world populations stand in serious need of protection from the possible abuses of research, on account of their sundry vulnerabilities (Benatar, 2000; Benatar and Singer, 2000). Even in the industrialized developed world, like anywhere else, in human affairs, it is not easy to avoid taking advantage of and exploiting the weak, needy, poor, sick and ignorant. And if we look at the history of scandals, abuses and atrocities in medical research (Emanuel et al., 2003), in conjunction with contemporary malpractices, then there is every reason to emphasize and insist on protection for research subjects in the developing world.

Many biomedical research studies in the developing world, particularly in Sub-Saharan Africa, have not been able convincingly to fulfill some of the requirements for ethical conduct of research on human beings, such as the informed consent condition, but have gone ahead, nevertheless. There is therefore a catalogue of recent scandalous and abusive studies that can be cited as having violated various putative ethical requirements or other ethical imperatives. These include but are not limited to the Trovan case in Nigeria (Macklin, 2003), the Nyumbani Orphanage case in Kenya (Walgate, 2004): the Dead Children's case in Malawi (Lemmens and Nwabueze, 2007; Mfutso-Bengu and Taylor, 2002), and the Tenofovir case in Cameroon. These and many other such cases are discussed in the discussion forum of the website of the African Malaria Network Trust (AMANET) (http://www.amanet-trust.org). Moreover, biomedical research in the contemporary world has become big business and, where big business, driven by economic power and the profit motive are at play, ethics, justice and fair play are always likely to be swept under the carpet (Lurie and Wolfe, 2007).

3. Ensuring the protection of research subjects

To ensure the protection of biomedical research subjects in the developing world, a certain framework, which is quite evident in the case of research in the developed world, is necessary. First and foremost in such a framework is rigorous scientific and ethical review of research protocols before they are approved for carrying out on the field. Rigorous scientific and ethical review of research protocols has become routine practice in the developed world but, while review is increasingly becoming at least a formal requirement in the developing world, such review often lacks rigor owing to inadequate infrastructures, resources and capacity (Nyika et al., 2009). Secondly, there is the need for appropriate supporting legal, human rights and advocacy structures. Regulatory frameworks for ethics in medical research are necessary at several different levels. A visual model for such a system of regulations would look like concentric circles, with the widest circle representing well-formulated international guidelines and the smallest circle delimiting the standard operating procedures of local or institutional ethics review committees (Tangwa, 2004).

The law is a sub-set or derivative of ethics, because the general end and purpose of the law is to serve the ethical principle of justice. But the law does not always serve the ends of justice, let alone those of ethics. The law in every society is made by those in power and sometimes it is made to serve interests other than those of ethics and justice. In Nazi Germany, for example, many oppressive and morally highly obnoxious laws were made. It is therefore not a justification of any policy that it is legal or even that the law has been made by a democratic government and has been upheld by its highest courts (Cook et al., 2003). For this reason, human rights have developed as the inter-phase between ethics and the law. The Universal Declaration of Human Rights (UDHRs) elaborated under the auspices of the United Nations Organization (UNO) in 1948 forms the basis of modern human rights. The UDHR was a reaction against the unethical laws of the German government which facilitated Nazi war crimes, culminating in the Nuremberg Trials and the Nuremberg Code.

These supporting structures are the central pillars of the developed Western societies but they are still to take firm roots in many developing countries. In Sub-Saharan Africa, few are the countries where human rights are observed in practice in a credible manner. Thirdly, there is the need for an enabling liberal and democratic environment, which is taken for granted all over the developed world but which is still to become a reality in many developing countries where, moreover, there is still lack of adequate awareness about what medical research is all about. Research carried out under authoritarian systems is bound to borrow some of the attributes of the operative system.

Direct responsibility for the ethical conduct of medical research on humans falls on four categories of persons: scientists who design and carry out the research, ethics committees or review boards which study and approve research protocols, sponsors and funders who provide the means and resources for carrying out research, and host and sponsor county authorities who permit and enable research to be carried out. Of these, more direct and immediate responsibility falls on the researcher–scientists or investigators who are in day-to-day contact with the research subjects on whom they perform the investigative procedures and manoeuvres. The principal investigator (PI) in any research project carries the heaviest responsibility for its ethical conduct.

4. Exploiting vulnerabilities

The exploitation of human vulnerabilities has been abundantly manifested in coercive research, deceptive research and inducive research. Coercion achieves an aim or objective through blatant or subtle threat of a harm perceived by the victim as greater than compliance. Coercive research is perhaps the most unethical type of research imaginable; it is arguably equivalent in moral obnoxiousness to research on completely innocent subjects who have not the faintest idea of what is going on. Most of the historical abuses and atrocities involving experimentation on human beings (Emanuel et al., 2003) involved coercive research. Although it would be hard to come across cases of blatant coercion in research today, subtle coercion is not yet absent from research and nearly all the examples cited above of scandalous research in Africa also involved subtle coercion, inasmuch as some of the subjects would have perceived non-participation as a greater evil than participation.

Next in moral gravity to coercive research is deceptive research. In deception the victim is made to misread or to misunderstand a situation, to have an illusion, delusion, mirage, etc. Deceptive research not only is quite possible but abundantly exemplified today, particularly in Sub-Saharan Africa. All the scandalous studies discussed above also involved deception in one respect or other, to a higher or lower degree. All research involving the so-called "therapeutic misconception" (where investigative procedures may be presented to appear to the subjects as therapeutic), "therapeutic illusion" (where in spite of explanations to the contrary research subjects themselves stubbornly believe investigative procedures and products to be necessarily therapeutic), research without or with inadequate informed consent are varieties of deceptive research. The remedy for deceptive research lies in thoroughly and adequately well-informed research subjects combined with procedures that respect the four cardinal principles of autonomy, beneficence, non-maleficence and justice.

Closely following behind coercion and deception for the bronze medal in moral obnoxiousness is inducive research. An inducement is something offered with the intention and purpose of making someone act against their better judgment or doing what they would otherwise not have done. Inducement is a serious problem in present day research especially in the developing world. It cannot properly be fully appraised without taking into consideration the distinction between the agent/patient of moral action. A high burden of disease, combined with desperate poverty and ignorance makes people highly vulnerable to inducive research. Too much enthusiasm to participate in research may be a sign that inducement rather than informed consent is at work, for even if it be granted that research subjects often access healthcare and treatments which they would otherwise not be able to access, it cannot be assumed that they would still be willing to subject themselves

to research if they could access such benefits in normal healthcare.

Inducing rather than rationally persuading subjects to participate in research is always ethically wrong. Deciding whether something, an offer, a benefit, or even a due, is an inducement can be appraised only in situ within a particular context. This is similar to the issue of whether a double standard is being applied or only a different standard (Tangwa, 2001). As moral agents we can guess what would induce the patients of our actions to behave in various ways, but we will never know for certain why people act/behave the way they do. But we always know for certain when we pose an act with the intention and purpose of achieving a specific end. From the point of view and perspective of the agent, inducement is completely knowable and completely avoidable, and this is all that matters from that point of view. You know very well when you are throwing corn to feed the chicken and when you are throwing it as a bait to catch it and cut its throat; while the chicken may not know the difference. From the point of view of the patient, of course, the patient also has the moral duty not to allow him/herself to be induced rather than rationally convinced. No moral agent can perform another's moral duties.

A distinction has usually been made between "due" and "undue" inducement (Emanuel, 2004; CIOMS, 2002, Guideline 7). The explanation underlying the distinction is that sometimes reimbursements to study participants for lost earnings, travel costs and other expenses incurred in the course of taking part in a study or other non-monetary benefits connected with the study may be so attractive to them as to cause them to join the study against their own better judgment. The distinction may be ill advised; for once it is admitted, it would be legitimate to ask when an inducement is rightly *due* to a research subject and how this is different from compensation or recompense. If it were admitted that a "small" inducement may be permissible while only a "big" inducement is unacceptable, the question naturally arises as to how small an inducement should be to be appropriate. Should the answer to this question not be "Small enough to induce?" But, in that case, why is a big inducement objectionable, since it would equally induce and, in addition, benefit the subject more?

Compensations, reimbursements and deserved benefits may, of course, under certain circumstances, induce potential research subjects. This is a serious matter which ought seriously to be addressed in contexts and situations where it obtains. A distinction can thus be made between "dues" and "inducements". But the distinction between "due" and "undue" inducements ought to be abandoned. An inducement is an inducement and cannot be "due" to a research subject. Having been coined by some of the best minds of the developed world, however, it is highly unlikely that the meaningless distinction (due inducement/undue inducement) will be abandoned. More likely will any calls for its abandonment be attacked with fulsome scholarship and charges of lack of understanding, engendering countless publications and a robust literature which anyone would be required to read and cite before taking a position on the issue. Research subjects should be reimbursed or compensated for whatever, with due care taken to ensure that this is not inducive; they should never knowingly be induced into the research.

5. Another type of deception in research

In social science research, there is a type of deception that is considered legitimate. This is in cases where the research question is such that giving adequate information about it to potential participants would countermand the results through conscious or unconscious behaviour change. A researcher who is investigating, say, wife bashing or child abuse in a community is likely to obtain false results through behaviour modification if s/he explains fully and completely the object and purpose of the research to the potential participants. In such cases, it is argued that it is permissible to withhold some information from the participants until the end of the research. At the end of the research the whole strategy is then disclosed to the participants in a process termed "debriefing". Even this type of apparently justifiable deception is controversial. It is arguable if such type of research really can achieve any results of value and even if it can it could further be argued that the duty not to deceive supersedes such value. But it is hard to imagine any situation in biomedical research where it would be ethically justifiable purposely to deceive or withhold information about the study from study participants.

6. Conclusion: Kisumu declaration

Developing world populations, particularly those of Sub-Saharan Africa, are highly vulnerable in medical research which has witnessed an exponential increase in recent years for various reasons. While much of this research is easily justifiable as aiming to serve the urgent health needs of the populations subjected to it, care must be taken to avoid harming, exploiting or otherwise treating research subjects in ethically unacceptable ways. The research scandals that have been witnessed in recent times in countries such as Nigeria, Kenya, Tanzania, Cameroon, etc. show that the protection of research subjects, particularly in Sub-Saharan Africa, is an important ethical imperative whose observance cannot be taken for granted. So let me conclude this paper with the *Kisumu Declaration*; so-called because it was proposed by me during the very first AMANET Health Research Ethics Workshop in Kisumu, Kenya, and enthusiastically adopted by all the participants. The Declaration could serve as the solemn undertaking of all stake-holders in any research project. Like other ethical guidelines, the Declaration, of course, can have only moral authority. It has no sanctions attached because it has no legal binding-ness, unless it was to be incorporated into the laws of some legal system. But it is enough that it has rational persuasiveness and moral authority. Whatever is done out of rational compulsion and moral concern is done with better reasons and firmer justification than what is done out of fear of sanctions.

6.1. Kisumu declaration of moral intergrity and noble intent

"We, the investigators, sponsors and funders of this study/research, hereby solemnly declare, on our honour, that our intentions in carrying out this research are noble and primarily motivated by the desire to acquire knowledge that could help in alleviating suffering and improving the lot of human beings, without any distinction or discrimination; that we have no overt or covert intention or any hidden agenda to harm, deceive, exploit or unfairly to treat, now or in the future, any human being or group of human beings. We solemnly pledge that, in carrying out this research, we will maintain the utmost respect for all participants and experimental subjects and objects, including any plants and animals. We will do everything within our powers to prevent knowledge gained through this research from being abused or used in ways contrary to the above solemnly declared aims and intentions."

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