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Special populations: vulnerability and protection

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Abstract
Research with vulnerable participants raises a number of challenging issues for researchers and ethical review committees. Vulnerability arises when participants are relatively powerless compared with researchers. This may be due to extrinsic factors such as poverty or lack of education, or intrinsic factors such as severe illness or intellectual disability. Vulnerable participants risk increased harm from research because they are unable to protect their interests. This article provides examples of research with vulnerable populations and describes in detail ways in which researchers and ethical review committees can work to decrease the risks of harm for these groups. Also, the article presents a discussion of sharing research benefits fairly, and describes four conditions for ethical research with vulnerable participants.

Keywords
research ethics; vulnerable populations; voluntary consent; fair benefits; harms

Introduction

Vulnerability can be broadly defined as the inability to protect one's interests (CIOMS 2002). The problem with vulnerability in relation to biomedical research is that vulnerable individuals or populations are at increased risk of being harmed due to a decreased capacity to protect their interests. Vulnerable participants can be harmed by coercion, inadequate informed consent, exploitation, and exclusion from research and its benefits. All research has the potential to cause harm, and all research participants are potentially vulnerable to some extent, especially those with ill health who participate in research with the expectation of receiving some therapeutic benefit.

Vulnerability exists upon a spectrum, rather than being either present or absent. However, it is possible to identify individual and groups who are *particularly* vulnerable in research, and at significant risk of harms. This article discusses vulnerability as a central issue in the debate about research ethics, since it is related to power inequities

in the relationship between researcher and participant. Persons or populations who are generally vulnerable through impoverished material circumstances or through diminished mental capacities are *prima facie* vulnerable, not only to researchers, but also in other relationships.

Others may not be generally vulnerable, but have become so through specific circumstances. The parents of a premature infant, for example, may be vulnerable to forced recruitment into research because they fear for the care of their child should they refuse. No matter how the power inequity arises, there is potential for harm in the relationship between research participants, on the one hand, and researchers and research sponsors, on the other hand. Researchers or research sponsors may, inadvertently or intentionally, take advantage of this power inequity to coerce participants to take part in research which is not in their best interests, or to avoid fairly sharing the benefits of the research with the research population.

This article proposes a classification of the different expressions of vulnerability: the extrinsic and the intrinsic ones. Also, it discusses the challenges of research with vulnerable populations and how informed consent form can be a mechanism for the protection of the interests and rights of research participants. Finally, the article analyses how coercion, paternalism, and protection should be balanced in the evaluation of research projects with vulnerable individuals or populations.

Extrinsic and intrinsic vulnerability

There are many sources of vulnerability, but it is helpful to establish a basic classification: a) extrinsic vulnerability - due to *external circumstances*, such as lack of socio-economic power, poverty, lack of education, or lack of resources; and b) intrinsic vulnerability - due to features to do with the *individual* themselves, such as mental illness, intellectual disability, severe illness, or the extremes of age (children and the elderly). These two types of vulnerability, extrinsic and intrinsic, both raise ethical issues in relation to participation in research. They may occur separately, or together. In particular, people with intrinsic vulnerability are often also extrinsically vulnerable as they usually lack power and may live in poverty and without access to education.

Vulnerability may apply to individuals or to populations. Many of the ethical issues raised by research with the vulnerable relate to populations. Consider, for example, the proposed trial of Surfaxin in Bolivia (Lurie & Wolfe 2001). The study population of premature babies born in Bolivia with respiratory distress syndrome was vulnerable as a *population* because they had no access to equivalent health care outside of the proposed trial. The community from which the research participants were to be drawn lacked access to surfactants and the intensive care facilities necessary for the survival of these babies. Participation in the trial afforded the only mechanism for accessing treatment for affected babies. Similarly in the zidovudine (AZT) trials in Africa, the population was vulnerable because they lacked access to antiretroviral therapy (ART) outside of the trial (Annas & Grodin 1988). In this case, the mothers knew that a baby born with HIV but lacking access to ART would have little chance of survival. Trial participation provided a chance of access to AZT and the possibility of preventing mother-to-child transmission of the HIV virus.

Both of these populations were extrinsically vulnerable, because poverty and lack of access to health care gave rise to power inequities in the relationship between researchers and participants. This extrinsic vulnerability was exacerbated by intrinsic vulnerability caused by having the health problems in question - prematurity in the first case and HIV/AIDS in the latter case -, leading to the need for treatment that was otherwise unavailable. It is common for both types of vulnerability to coexist.

Extrinsic vulnerability

Extrinsic vulnerability derives from the socioeconomic context in which research participants live. Unjust social circumstances can give rise to vulnerability in a number of ways, each of which requires different mechanisms to protect the research population from exploitation and harm.

Lack of power

Extrinsic vulnerability occurs where certain groups are unjustly denied social and political rights. This category of vulnerability is referred to as "lack of power". Groups may be subject to institutionalised discrimination on the grounds of gender, race, age or sexuality. Institutionalised discrimination can force affected groups into a subordinate position within the social hierarchy. In many parts of the world, women suffer from this form of vulnerability because they live in patriarchal social structures that deny their right to self-determination. Indigenous peoples are also liable to discrimination from dominant social groups. Structural discrimination and subjugation can result in victims believing they are inferior to other members of the community and therefore assuming that they do not have a right or capacity to decide for themselves about whether to participate in research.

Populations who are treated, and who may also view themselves as subordinate, are vulnerable both to explicit and implicit direction from those in positions of power. In some parts of the world, for example, women may not be permitted to participate in research without the *explicit* approval of either husbands or fathers. Researchers should also be aware that such vulnerable groups may interpret the invitation to participate in research as an *implicit* directive from a medically trained official.

Populations who are vulnerable because of a lack of power in their community are more likely to be exposed to additional risks as a result of participation in biomedical research, over and above the standard health risks. There are a number of recognised risks in any research (Weijer 2000):

• physical risks, such as bodily harm and physiological disturbance – minor or serious, temporary or permanent, immediate or delayed;

• psychological risks, such as affecting the research participant's perception of self, emotional suffering (for example, anxiety or shame), or aberrations in thought or behaviour;

• social risks, if participation in the study or the research findings expose participants to the discrimination, or other forms of social stigmatization;

• and economic risks, if participants have to directly or indirectly bear financial costs related to research participation.

These risks are exacerbated in research with vulnerable participants. If research involves investigation into stigmatised diseases, such as HIV/AIDS or stigmatised practises such as homosexuality, prostitution, or injecting drug use, the risks to research participants can be significant. The HIV/AIDS pandemic still ignites substantial fear and prejudice throughout the world, particularly in resource-poor settings where there is no treatment available. Taking part in a clinical trial increases the chances of a participant's community finding out that an individual is HIV-positive. Persons infected with HIV have been ostracized by their families and communities, evicted from their homes, rejected by their spouses, and in some cases been the victims of physical violence and even murder (Unesco 2003). Researchers must be aware that the risk of discrimination and social exclusion can represent a significant burden for participants.

Research participation can also have negative psychological effects on vulnerable trial participants. Unaids – Joint United Nations Programme on HIV/AIDS - is a program of the United Nations created in 1996, whose role is to come up with solutions and help the nations to fight HIV/AIDS. This program notes that participation in a complicated, lengthy trial involving intensely intimate matters to do with health and sexuality and exposure to culturally different scientific and medical concepts and process may cause anxiety and depression, as well as stress between partners in a relationship (Unaids 2000). Finally, trial participation may be harmful for research subjects who are allocated to the control arm of a placebo-controlled trial and who are therefore exposed to the psychosocial risks of research participation without actually receiving active treatment.

Box 1 - Issues arising from lack of power

Likely harms
- Coercion
- Inadequate consent
- Increased risks of harms

Potential remedies
- Informed consent with attention to increased risks
- Capacity building (resources and education)
- Confidentiality
- Attention to non-physical risks

Educational disadvantage

Poverty can mean that potential research populations have received minimal formal education, may be illiterate, and are likely to be unfamiliar with technical concepts associated with clinical research. Unfamiliarity with key concepts of clinical research and illiteracy can present barriers to obtaining adequate informed consent from the research population. For example, many languages have no direct translation for words like "placebo" or "randomisation". Translation of these concepts into local languages can lead to confusion and controversy (Achrekar & Gupta 1998; Limpakarnjanarat & Chuachoowong 1998; Pichayangkura & Chokewiwat 1998).

It is important to recognise the difference between diminished capacity to provide informed consent as a result of limited cognitive capacity – for example, children, those with cognitive disabilities or acute psychoses – and the challenges associated with gaining informed consent from populations with full cognitive capacity but with limited education and/or illiteracy. People without full cognitive capacity may require guardian consent in addition to their own consent. Illiterate or uneducated populations, on the other hand, do not typically require guardian consent as they posses the cognitive capacity to determine which course of action best protects their interest. These populations should not be treated paternalistically; rather research sponsors should invest time and resources in developing communication strategies that facilitate full informed consent.

Box 2 - Issues arising from educational disadvantage

Likely harms
- Inadequate consent
- Coercion

Potential remedies
- Consultation and communication with community
- Special informed consent mechanisms and materials
- Capacity building (education)

Lack of access to basic health care

Lack of access to basic health care is a form of extrinsic vulnerability, which overlaps strongly with intrinsic vulnerability. The vulnerability that co-occurs with lack of basic resources is exacerbated when people become ill or require health care. The sheer extent of unmet health needs in many developing countries, combined with poverty and social deprivation, makes populations, particularly those who are sick, highly susceptible to exploitation or coercion in research (Unaids 2000; CIOMS 2002; London 2005). It is clear that many research participants in resource-poor countries without access to universal public health care join clinical trials

in order to get basic medical treatment. This causes concern because it may a) undermine the voluntariness of the participants' consent; and/or b) lead research participants, out of desperation for health services, to agree to participate in research that does not provide them with a fair share of the benefits.

Box 3 - Issues arising from lack of access to health care

Likely harms
- Coercion
- Exploitation

Potential remedies
- Capacity building (resources)
- Fair benefit sharing post trial

Intrinsic vulnerability

Intrinsic vulnerability comes from specific features to do with individuals or populations. This may be the existence of a mental disability or illness which impairs a person's capacity to make decisions. It may also be the occurrence of a life-threatening illness, either in the person themselves or in someone they are responsible for, such as a child or aged relative. Babies and young children are intrinsically vulnerable as they are unable to protect their interests and must rely upon others to act for them. The elderly may become vulnerable if they are very frail or lose their mental capacities.

In all of the groups, it is important to consider, on a case by case basis, whether or not individuals can give consent, and if not, how much information they can understand, and who else must be consulted or is legally entitled to give consent for them.

Babies and children

Babies and children lack the intellectual capacity to understand what research involves and the reasons for it; therefore, they are not able to give informed consent. In these cases guardians must decide whether research participation is in the child's best interests and are responsible for providing informed consent. Child participants should be provided with age-appropriate information.

Older children and adolescents

The capacity to understand and consent to research is something which develops gradually as the child matures. It does not appear overnight when the adolescent reaches the legal age of consent. Older children and adolescents have a right to have the research explained at an age-appropriate level, and they have the right to refuse to participate. In most cases it is therefore appropriate to require the consent of the legal guardians *and* the assent of the child/adolescent, which involves explaining the research to the level possible and seeking agreement from the child.

Children may be at risk of coercion or exploitation from adults to participate in research. This pressure may come from their parents, peers, teachers at school or other adults who have authority over the child. This makes some of the issues raised by research with children similar to those raised by research with participants who lack power more generally. In addition, there may be conflicts of interest between the child and their parents or legal guardians. Research into sexual or physical abuse within the family, for example, may be in the interests of the child but not the parents if they are perpetrators of violence. If researchers wish to conduct research without the informed consent of the guardian they must demonstrate to the research ethics committees that a) the child or adolescent participants are of sufficiently maturity to provide consent themselves; and b) that requiring guardian consent would significantly impede the goals of the research.

The desire to protect both young and older children from harm may result in their exclusion from research that is potentially of benefit either to the children involved, or to other children in the future. It is important that children's intrinsic vulnerability does not become a barrier to valuable paediatric research. With age-appropriate assent/consent procedures, and context-appropriate child and guardian consent, paediatric research can be ethical and beneficial.

Mental incapacity

Mental disability may arise from a cognitive impairment, such as dementia, an intellectual disability, such as Down syndrome, or a mental illness, such as schizophrenia or severe depression. The main ethical issues raised by mental incapacity are to do with consent to participation in research, and potential exclusion from research. Understanding the proposed research is a crucial part of giving consent. People with mental incapacity may have varying abilities to understand the information necessary to give a valid consent to participate in research. This ability may fluctuate in relation to the time of day and administration of medication, duration and nature of illness, the individual's discomfort or distress, and the complexity of the research.

Because it may be more difficult to obtain informed consent from people with mental incapacity, they can be excluded from research which would otherwise be beneficial. This is particularly important in relation to mental illness, which often coexists with physical illness, making it important to gather research data on the effects of treating multiple illnesses in the same person. As with other vulnerable groups, research participants with mental incapacity may be at increased risk of harm if they are unable to understand the reasons for any discomforts or changes in routine associated with the participation.

People highly dependent upon medical care

People highly dependent upon medical care include patients who are unconscious, in intensive or high level

care units, those receiving emergency care, and some terminally ill. This group is vulnerable because such patients are in urgent or potentially life-threatening situations and are dependent upon medical care for even limited survival. This makes them vulnerable to coercion as they do not have the time or capacity to consider other options for their care and may be fearful of jeopardizing their treatment by refusing a research request from those who are providing their care.

There are issues to do with understanding as many in this group may be unconscious or, if conscious, may not be able to understand or focus on the necessary information to give consent for participation in research due to the stresses of their illness. Some people in highly dependant groups may feel that participation in research offers the only chance for survival, for example research into treatments for advanced cancer. There may be time pressures in emergency situations, which limit the opportunities to properly explain the research.

Exclusion of prospective participants from research, due to lack of capacity to consent, is also a problem for people highly dependant upon medical care, as it can result in unproven therapies or limited innovation in treatments for this group.

Box 4 - Issues arising from intrinsic vulnerability

Likely harms

- Inadequate consent
- Coercion
- Exploitation
- Exclusion

Potential remedies

- Adapted informed consent or assent
- Guardian consent
- Fair benefits
- Fair inclusions

Issues requiring special consideration with vulnerable populations

Informed consent: understanding

Consent is one of the major challenges posed by research with vulnerable groups. Consent must be adequately informed. This requires that potential participants have sufficient information and adequate understanding of both the proposed research and the implications of participation in the study. In an investigation at the National Women's Hospital in New Zealand, the women were not told that they were part of a research trial, and thought that they were receiving standard care. They were not provided with any information on the researcher's experimental hypothesis about cervical cancer, and did not understand that they were being placed at increased risk because they were not receiving the usual surveillance, monitoring or treatment for cancer of the cervix. Lack of information was also a problem in the Trovan trial. Parents of children involved in the trial claim that they were not told that this was a research trial rather than regular treatment, and they were not told that they could receive free treatment provided by Medicines Sans Frontiers without being in a research trial.

When the population is vulnerable, special efforts are necessary to ensure that potential participants understand basic information about the research. If vulnerability is due to educational disadvantage, research sponsors must take a number of steps to help with understanding. First they must find out the level of education or understanding in the potential trial population to determine their informational needs. Next, they must devise special strategies and develop appropriate tools such as booklets, video clips and role plays, to ensure that the research population understands the risks and benefits of research participation (Kilmarx 2001). This process can be lengthy, but it is a crucial part of seeking informed consent. Community advisory panels can provide context-specific advice about recruitment and appropriate trial conduct (Kilmarx 2001). For example, research ethics committees in Australia refer proposed research involving indigenous populations to Aboriginal and Torres Straight Islander advisory committees for comments and approval.[1]

Research participants with limited mental capacities may not be capable of understanding detailed information about the research protocol, but depending upon the level of disability, may be able to understand key features of the proposed research (Fisher et al. 2006). Efforts should be made to communicate at an appropriate level, using communication tools and strategies designed to help achieve understanding. With children, it is important to provide them with as much information as they can understand, at a level appropriate to their age. It should be considered whether the children participants are likely to be able to give consent, or whether their parents should be consulted. The important factors to consider are the age of the children, the nature of the research – invasive or not –, potential harms and benefits, and any conflicts of interest between the parents and the children.

For participants who lack the capacity to understand information about the proposed research, it is usually necessary to seek consent from another person, either their legal guardian or a relative who has the power to make decisions for the participant. The person making the decision needs the same information about the research as a participant would. If there are any legal regulations about guardians and research, these should be obeyed. As the information required to understand a research project may be complex, it is possible to break them into two stages. In the first stage, potential participants should be provided with basic information about the research, including the purpose, methods, demands, risks and potential benefits.

Box 5 - First stage information for adequately informed consent

- Purpose: what will the research find out?
- Methods: how will it do this?
- Demands: what will happen to the participant?
- Risks: what harmful things might happen?
- Potential benefits: what beneficial things might happen?

This information should be presented in ways that are adequate to the educational level and intellectual capacities of the potential participants. It may be appropriate to allow a period of time, for example a few days, for them to consider this information and discuss it with family or friends, before deciding whether or not to receive more information, or refuse to participate. Once participants have had a chance to consider the first stage information, there are further issues that should be discussed before giving informed consent.

Box 6 - Second stage information for adequately informed consent

- How will privacy and confidentiality be protected?
- Are there any alternatives to participation?
- How can participants withdraw from the study if they want, and what will happen after withdrawing?
- How will the research be monitored and by whom?
- How can participants make a complaint?
- How can the researchers be contacted?
- Who is funding the study, how much, and are there any conflicts of interest for the researchers, sponsors or institutions?
- Are there are any payments to participants?
- Are there any expected benefits to the wider community?
- How will the results be disseminated?

Researchers should ensure that they have prepared answers to all of these questions in forms that can easily be understood by the participants. For potential participants with limited mental capacity, it may not be possible to explain all of these details to those involved. In that case, this information should be provided to the guardian or carer of the participants. In the case of emergency research, the information should be provided to the participants as soon as possible after they have recovered from the emergency.

Voluntary consent: coercion

For consent to be ethically valid, it must be voluntary. This means that the person or group giving consent are free to make a decision to participate or not to participate, without being put at a disadvantage or in any other danger. Vulnerable populations, especially those who lack power and/or access to basic medical care, are at increased risk of coercion. Those who lack power may not have the capacity to refuse participation in research due to fears about the consequences of a refusal, such as direct or indirect punishment, or further discrimination. When the lack of power is due to structural social factors, it can be difficult to ensure free decision making, but there are ways to support vulnerable individuals or groups in coercive situations.

An independent advocate can act as an intermediary between authority figures and the participants. For the advocate to be credible, they should be clearly independent from the research project; for example, they should be paid to provide advice and support, rather than paid for each person who enrols in the trial. Coercion can occur when there is an established relationship with a power imbalance, for instance in research carried out by practitioners on their patients. Patients may fear offending their doctor, or prejudicing their ongoing care if they refuse to participate. Again, independent advocates can help in this situation. Assurances about the voluntary nature of the research and high standards of confidentiality are also ways of trying to reduce the coercive effects of lack of power.

The desperate circumstances of those who lack access to basic medical care may give rise to questions about the voluntariness of their consent into research if they see no alternative way of accessing medical care. In the AZT trials and the planned Surfaxin study, the participants all lacked access to such care, making it more likely that they would agree to be in the research. It is particularly important to ensure that there is information about any alternative access to medical care, and that the participants have a realistic view of the care that they will receive.

Reciprocity: providing fair benefits for vulnerable research populations

One of the key concerns associated with the recruitment of vulnerable populations for research is that they will not fairly share in the benefits of the study. Extrinsic vulnerability emerges out of unjust social systems, where some parts of the populations are denied equal social, economic, and political rights. Research sponsors, particularly well resourced and powerful sponsors from developed countries who conduct research with vulnerable populations, have an obligation to invest in local capacity building in order to ensure that the population derives fair benefits from the research endeavour. Capacity building should address the underlying sources of the vulnerability, thereby reducing the community's future vulnerability. Support for capacity building can be found in international guidelines, reports and papers that have called for increased investment in trial-related capacity building in developing countries. The Council for International Organizations of Medical Services (CIOMS 2002) takes a broad perspective on what counts as research-related capacity building.

Box 7 - CIOMS capacity building

Capacity-building may include, but is not limited to, the following activities:

- establishing and strengthening independent and competent ethical review
- strengthening research capacity
- developing technologies appropriate to health-care and biomedical research
- training of research and health-care staff
- educating the community from which research participants will be drawn.

While the need for capacity building in host communities is generally recognised and accepted within the international research community, there remains significant uncertainty about the specific level of investment required. The results of Kass and Hyder's research (2001) into the experiences and attitudes of researchers involved with international research showed 94% of respondents indicated that at least one capacity building resource or research infrastructure would remain in the country after their study was over. However, these capacity building initiatives vary enormously in terms of their size and the population who derives direct benefit from them – the benefits range from pharmaceutical supplies, to office equipment, to data management systems, to the training of personnel (KASS & Hyder 2001). At the moment there is no standard protocol for determining whether the proposed capacity building initiatives provide vulnerable populations with a *fair* share of benefits.

Exploitation and inducements

Exploitation occurs when the benefits of a cooperative activity, such as research, are unfairly distributed between the parties. Inequalities in bargaining power between the parties allow the researchers or research sponsors to derive a disproportionately large share of the benefits of the research endeavour, at the expense of vulnerable participants. Both extrinsic and intrinsic vulnerability can be exploited.

It is important to note that even exploitative research can sometimes be beneficial for the subjects, because they are often better off than they would otherwise have been. Even if the vulnerable party does not receive *fair* benefits, they may receive *some* benefit from research participation. Exploitation can also be consensual. When an individual or community is extrinsically vulnerable due to desperate circumstances, such as poverty and illness, it can be rational for them to voluntarily agree to arrangements that, although unfair, represent the best available alternative. Exploitation that is both beneficial and consensual is still unethical because it fails to provide research participants with their fair share of the benefits of research.

Research sponsors should be encouraged to consult with vulnerable populations in the planning phase of the study to determine what research associated benefits the participating community would value. If researchers work in partnership with vulnerable populations, respecting their interests and values, the potential for exploitation is significantly reduced. Nonetheless, benefits are not fair simply by virtue of the fact that research populations have agreed to accept them.

Calls to decrease exploitation by offering greater benefits for trial participants from vulnerable communities have been countered with concerns that such benefits may result in undue inducement (Unaids 2000; CIOMS 2002). It has been argued that benefits over and above those necessary to carry out the research should not be so large, or the medical benefit so extensive, as to induce prospective subjects to consent to participate in the research against their better judgement (CIOMS 2000). Benefits are thought to be undue when they distort the judgement of potential research subjects and undermine the voluntariness of their consent (Grady 2001). The paternalistic argument against inducements is that they will encourage subjects to volunteer for research against their best interests (Mcneill 1997; Wilkinson & Moore 1999). There is a general fear that potential participants would be "blinded" by the benefits offered and might therefore underestimate the risks of research, overestimate the benefit of the cash payment, or weight the risks adequately but decide to act against their best interests in order to access the payment (Wilkinson & Moore 1999).

There is thus an apparent clash between preventing exploitation by providing fair benefits and preventing undue inducement by offering payments (Macklin 1989). Offer participants too little, and they are exploited; offer them too much, and their participation may be unduly induced. Some have argued that the more vulnerable a research subject is, the greater the risk that additional benefits will act as an undue inducement (Resnik 2001). It is necessary to decide at which point the benefits offered to research subjects stop being fair benefits and risk becoming an undue inducement. The point at which this line is crossed will vary depending on the research population in question.

This is a difficult decision if one is not familiarized with the specific socioeconomic circumstances of the proposed research population; in such cases, one should endeavour to consult with the relevant community representatives, considering the acceptability of the benefits offered to research populations is complex. There is increasingly ethical debate about whether ethics committees should paternalistically deny research participants fair benefits. The increased controversy is in part due to the fact that financial inducements to motivate risky behaviour are thought to be acceptable in various other fields, such as danger money for jobs involving higher than normal risks (Morton 1991; Menikoff 2001). If populations are extrinsically vulnerable because they have historically been denied just access to medical care, education or social status, it seems doubly unfair then paternalistically to deny such populations access to what would otherwise be considered fair benefits for their research participation.

Issues in international collaborative research

The last few decades have seen a rapid expansion in the outsourcing of clinical research to developing countries. A 2005 survey conducted for the Commission on Intellectual Property Rights, Innovation and Public Health of the World Health Organization (WHO) indicates that the number of clinical trials in developing countries has increased tremendously over the last decade (Matsoso et al. 2005). For example, in 2004 GlaxoSmithKline announced that it planned to increase the percentage of clinical trials conducted in low-wage countries from 10% in 2004 to 30% in 2005 (Capell 2004). Since the AZT trials in the 1990s, such international research collaborations have consistently ignited controversy.

CIOMS (2002) defines international research as research undertaken in a host country but sponsored, financed, and carried out by an external international or national organization or pharmaceutical company. International research often involves multiple sponsors including one or more corporate sponsors, one or more national government sponsors, and one or more international agencies (Unaids 2000). The power differential between vulnerable populations in developing countries and research sponsors, including global pharmaceutical companies, from developed countries can be significant. Further, when research is sponsored by an external agency, it is often the case that the benefits of that research will be available in developed countries, but will not be shared with the research populations and host country. There is no simple mechanism for ensuring that research populations in developing countries will receive access to the benefits of the research endeavour. The Declaration of Helsinki states that

> […] it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review. (WORLD MEDICAL ASSOCIATION, 2004, Paragraph 29, note of clarification).

However, in practice very few research sponsors make a commitment at the beginning of a trial to provide access to interventions that are demonstrated to be safe and efficacious. Research sponsors may however provide different types of benefit to the research community and the ethics committee must consider the appropriateness of these benefits.

Fair participation and the research agenda

Harm can arise both when vulnerable populations are overly burdened with research, since they represent an accessible group, and when they are excluded from research. Research with these populations is ethically justified when it addresses a health concern of the population in question. This can be achieved by working collaboratively with the research community to establish the research agenda.

Just participant selection

Vulnerable populations should not be selected for research simply because they are accessible, open to manipulation or coercion, or unable to demand fair benefits. Many examples of unethical research, both historical and modern, concern cases where the research population was selected for the administrative convenience of the researchers and research sponsors rather than on medical grounds. For example, Pfizer conducted research into the antibiotic Trovan during a childhood meningitis epidemic in Nigeria because they had not been able to find sufficient children in the United States. Pfizer was in the area for only three weeks, did not track the long term progress of the participants and had no plans to ensure that the research community would have access to the intervention if the trial proved that it was effective.

Research should be conducted with vulnerable populations only where it is responsive to the health needs of the community in question and where there is a reasonable likelihood that the community will have access to the benefits of the research, whether the benefits are health knowledge or therapeutic products. Thus, research should only be conducted with children where it investigates a question of paediatric health or disease so that the paediatric population stands to benefit from any knowledge generated through the research.

Box 8 - Conditions for research with vulnerable populations

Research should only be conducted with vulnerable populations where:

- the research question posed is important to the health and well-being of the population;
- the study methodology is culturally and socially appropriate for the population;
- the research is conducted in a manner that seeks to protect the physical, emotional and psychological safety of the population; and
- any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population.

Adapted from National Health and Medical Research Council (1999) and CIOMS (2002).

Conclusion

Research participation is a valuable experience that should not be denied to individuals or populations simply because they are vulnerable. In addition to the personal benefit that may be derived from research participation, research with different populations is necessary to de-

velop medical and clinical knowledge about the aetiology of disease, and the safety and efficacy of medical interventions in these populations (Rogers 2004a). Women and children, for example, have historically been denied access to clinical trials on the grounds they represent vulnerable groups who should be protected from the risks of medical research.

In the absence of specific research with these populations, clinical treatment must be based on the results of studies with adult male research populations, despite importance physiological differences between men and women and between adults and children. This extrapolation can lead to both the under-treatment of women and children because there is a lack of clinical data demonstrating safe and effective options, and exposure to harm from unknown risks of drugs in these populations (Rogers 2004b). Providing that vulnerable populations are treated respectfully, share fairly in the benefits, and that the research addresses health concerns relevant to the population in question, research with vulnerable groups is a social good that should be encouraged and facilitated.

In order to ensure that research is responsive to the health needs and priorities of the research population, researchers must consult with those communities where research is planned. Where possible, community representatives should be integrated into the research planning process from an early stage. In this way the research population becomes an equal and active partner in the setting of the research agenda and the execution of the research, rather than a passive subject of the research. This approach is called community-based participatory research (CBPR). It is based upon a philosophy of collaborative research that recognises the unique strengths of all partners in the research, including research participants. CBPR provides scientific advantages because research designs that take into account the cultural context yield results that are more robust and more practically useful as they can be interpreted and applied with confidence. Models of effective CBPR have been demonstrated in research with indigenous populations and stigmatized populations such as drug users (Higgs et al. 2006; Quigley 2006).

Vulnerability is a key-concept in the reflection on research ethics. The two types of vulnerability, the extrinsic and the intrinsic ones, help understanding limit-situations. Finding a balance between paternalism, avoiding coercion, and protection in so unlike social realities is the great challenge to be reached in the ethical reviews of protocols of studies with vulnerable individuals or populations. Recognizing that the ethical aspects related to these populations are limited is an important step so that the outrageous clinical research episodes found in the history of research with human beings are not repeated.

Note

1. Aboriginal and Torres Strait Islander are two great Australian groups formed by aborigines and islanders from Torres Strait. Historically, several researches were conducted with these peoples, but they did not necessarily benefit from the results. In attention to this, the Australian government drew up, together with several groups and individuals, a document explaining the process of ethical health research to these communities. The objective was to instruct them in the decision to participate in research as well as in the defense of their interests and cultural values.

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