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# **Ethical challenges in study design and informed consent for health research in resource-poor settings**

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# EXECUTIVE SUMMARY

This review considers ethical challenges to research design and informed consent in biomedical and behavioural studies conducted in resource-poor settings. A review of the literature explores relevant social, cultural, and ethical issues in the conduct of biomedical and social health research in developing countries. Ten case vignettes illustrate ethical challenges that arise in international research with culturally diverse populations.

Professional and public debates concerning the application of guidelines for ethical conduct in studies carried out in developing countries are likely to continue as new information becomes available. Researchers in biomedicine, public health, and the social and behavioural sciences confront the challenging task of adhering to national and international regulations in social and cultural environments in which ethical guidelines may not be easily translated or applied. Increased awareness of ethical concerns associated with study design and informed consent among researchers working in resource-poor settings is needed. But strengthening professional knowledge about international research ethics is not enough. Investigators also require practical advice on the best methods or models for articulating ethical guidelines in the field. Empirical research on a wide range of issues relevant to the application of ethical guidelines is needed, including studies of macro social and economic developments that drive the globalization of the biomedical research enterprise. Technological and financial resources are also necessary to build capacity for local collaborators and communities to ensure that results of research are integrated into existing health systems. This requires collaborative efforts and engaged commitment on the part of investigators, funding agencies, policy-makers, governmental institutions, and industry.

Recommendations for researchers and policy-makers concerned about ethical practices in multinational studies conducted in resource-poor settings are listed below.

- **Respect the cultural traditions of study populations and communities**

Respect for cultural traditions builds a foundation of trust between researchers, study participants and the local community. Researchers should identify concerns that are culturally based and develop strategies for addressing them in a meaningful way. If possible, when protocol procedures require a transgression of local traditions and customs, investigators should consider developing alternative methods for achieving successful results.

- **Strengthen capacity for developing collaborative partnerships**

Collaborative partnerships must be strengthened between researchers in resource-rich and resource-poor settings. Capacity building should be a priority. Investigators should make efforts to strengthen the local health infrastructure and to provide for the continuation of effective research interventions and programmes. Collaborative partnerships should be developed between researchers, funding agencies in public and private sectors, governmental institutions, and private industry to consider seriously methods for reducing health disparities that exist between resource-rich and resource-poor communities.

- **Strengthen education in research ethics for investigators**

In many settings, educational opportunities in research ethics are often inadequate or non-existent. Training in research ethics should be strengthened for investigators in both resource-poor and industrialized nations.

- **Strengthen capacity for independent ethical review of protocols**

Ethical review of research protocols in resource-poor settings should be improved. Capacity building should include greater access to educational opportunities in research ethics for members of institutional review boards (IRBs) and ethical review committees (ERCs) in both resource-poor and

resource-rich countries. Particular attention should be given to the need to be cognizant of cultural differences in reviewing protocols for collaborative research. Responsibilities of multiple IRBs involved in a single project must be clarified to avoid confusion.

- **Develop culturally meaningful approaches to informed consent**

Researchers should develop culturally appropriate methods for obtaining informed consent. In some settings, sensitivity to local cultural context requires that investigators provide opportunities for individuals to seek advice or permission from a third person, such as a spouse or head of household. Researchers also may need to consult with local community leaders before implementing a study. In every situation, researchers should pay attention to ethical issues arising from the imbalance of power between researchers and participants. Researchers should be creative in designing strategies to ensure adequate comprehension of study goals, procedures, risks and benefits. This may require implementing educational interventions before consent or developing methods for determining an individual's comprehension of the study objectives.

- **Apply appropriate standards of care and provisions for medical treatment**

Researchers must consider appropriate standards of care in the design and implementation of an investigation and be ready to change the design if existing therapies become available in an area in which access to such therapies was previously denied to the study populations. Researchers should work collaboratively with funding institutions, governmental agencies, and pharmaceutical companies in developing strategies to provide effective therapies for participants during the course of a study and, if relevant, after a study has ended.

- **Provide ongoing feedback to the study participants and community**

Prompt and continuous feedback reassures study participants and their community that their participation in a research project is critical. Researchers should develop plans to disseminate information about the study and its results in ways that are culturally and linguistically meaningful.

- **Develop plans for resolving conflicts surrounding research implementation**

Researchers should carefully consider the potential for conflicts within the community that may occur during the course of the study or at its completion. This requires adequate knowledge about community dynamics and existing power structures before conducting a study. Often, conflicts may not or cannot be anticipated. When they happen, researchers should be flexible and creative in exploring all possible solutions.

## **Recommendations for research**

There continue to be gaps in existing knowledge regarding the application of national and international ethical guidelines for research with study populations and communities in resource-poor settings. Greater attention should be given to the development of theoretical approaches and analytical tools for assessing social and ethical challenges to planning and implementing biomedical and behavioural studies in developing countries. Descriptive empirical research is needed to determine normative behaviour and to promote the development of new ethical guidelines or revisions of guidelines that have been established. Future research should address the following issues:

- **Informed consent practices**

There is an urgent need for strategies to improve discussions on informed consent so that comprehension of study goals and objectives is enhanced in all cultural settings. Future studies should include assessments of how language, literacy, beliefs about decision-making authority, and beliefs about the nature of research influence voluntary participation and comprehension of information. Educational interventions to improve consent for biomedical and other health-related research should be developed and tested for linguistically and ethnically diverse populations in resource-



poor settings. Additionally, there is a great need for studies examining modified or simplified approaches to informed consent for research.

- **Community consultation for research**

Empirical research is needed on the process of community consultation for approval or permission to conduct a study. Researchers should consider how cultural, social, and political factors influence decision-making among individuals representing the local population. Attention should also be given to the implications of community consultation for expressions of individual autonomy, voluntary participation, and informed consent.

- **IRBs and ERCs**

Future research should address the constitution and decision-making processes of IRBs and ERCs in both industrialized and resource-poor settings. Strategies for strengthening their capacity to effectively and fairly evaluate research protocols for multinational studies in developing countries should be explored. Special attention should be given to the social and political dynamics that influence the “gate-keeping” function of review committees.

- **Collaborative research partnerships**

More information is needed on the nature and conduct of existing collaborative partnerships between researchers from resource-poor and resource-rich environments and effective strategies to strengthen these partnerships. What are the factors that contribute to a strong foundation for building collaborative partnerships between researchers from industrialized countries and developing countries? What resources are necessary to sustain a long-term collaborative partnership? How can researchers, academic institutions, private and public funding agencies, governmental authorities, and the biomedical and pharmaceutical industry cooperate to ensure that resources are available for effective collaborative partnerships?

- **Development of instruments to study ethical challenges in research design and implementation**

Survey questionnaires, interview schedules, and other instruments should be developed, tested, and validated for the examination of a range of factors that influence ethical challenges in research design and informed consent. Investigators could apply these research tools in the context of conducting formative research for the design of clinical trials or other biomedical and behavioural studies. These instruments could also be tested and validated as primary investigational tools in studies of the influence of social and cultural factors on ethical challenges surrounding research design or informed consent practices in ethnically and linguistically diverse multinational settings.

Robust empirical accounts of cultural, social and moral issues surrounding research design and informed consent must include not just an assessment of local beliefs about the nature and conduct of investigations, but also the broader social and political factors that influence and transform the globalization of biomedical and behavioural scientific initiatives.



# 1. INTRODUCTION

Scientific and technological developments in the prevention and treatment of disease depend upon the successful implementation of laboratory-, clinical-, and community-based research initiatives. Ethically sound research design and voluntary informed consent are universally accepted preconditions for scientific investigations involving human participants. National and international guidelines for ethical conduct in scientific research outline specific requirements for independent review of protocols, research design, standards of care, and informed consent (see Boxes 1 and 2). However, their applications in the field often pose considerable challenges for investigators, particularly in resource-poor environments.

## **Box 1. Selected international guidelines and recommendations for ethical conduct in research**

Council for International Organizations of Medical Sciences (CIOMS) (1991) *International guidelines for ethical review of epidemiological studies*

CIOMS (2002 [1993]) *International ethical guidelines for biomedical research involving human subjects*

Council of Europe (1997) *Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention On Human Rights and Biomedicine*

European Forum for Good Clinical Practice (1995, 1997) *Guidelines and recommendations for European ethics committees*

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (1996) *Guideline for good clinical practice*

Nuffield Council on Bioethics (2002) *The ethics of research related to healthcare in developing countries*

Nuremberg Code (1949) *From trials of war criminals before the Nuremberg military tribunals under control council law No. 10.*

UNAIDS (2000) *Ethical considerations in HIV preventive vaccine research*

WHO (2000) *Operational guidelines for ethics committees that review biomedical research*

World Medical Association (2000 [1964]) *Declaration of Helsinki: ethical principles for medical research involving human subjects*

Research design and informed consent are influenced by a range of factors: the goals and objectives of the study, the cultural setting in which the project is conducted, communication issues that affect comprehension of information, and discrepancies in social and economic power of the participants, communities, researchers and study sponsors. Investigators conducting biomedical and social health research face myriad ethical issues in any cultural setting. In poor environments throughout the world, ethical challenges are heightened owing to social and structural factors that contribute to inadequate resources for health services and research, ineffective health-care infrastructures, and health disparities. Inadequate resources, for example, can diminish opportunities for independent ethical review of protocols and may also limit the ability of researchers to maintain successful experimental interventions after completion of studies. Moreover, some individuals and communities may be vulnerable to exploitation or coercion in research because of their poverty or social status. In other settings, polit-

ical conditions negatively influence the potential for voluntary participation. Additionally, language barriers may inhibit effective communication, particularly regarding the translation of difficult scientific concepts. There also may be differences in beliefs about who is able to provide consent to participate in scientific research. The western paradigm for informed consent emphasizes the importance of individual decision-making, but in many non-western settings community leaders or family members play an important role in the decision-making process for participation in research.

## **Box 2. Selected national guidelines and recommendations for ethical conduct in research**

Committee on Research Involving Human Subjects (China) (1998) *Guidelines on ethical review of medical research*

Department of Health and Human Services (US) (1991) *Code of federal regulations Title 45 Part 46: Protection of human subjects*

Health Research Council of New Zealand (1997) *HRC guidelines on ethics in health research*

Indian Council of Medical Research (2000) *Ethical guidelines for biomedical research on human subjects*

Medical Research Council of the United Kingdom (MRC-UK) (1998) *Guidelines for good clinical practice in clinical trials*

Medical Research Council of the United Kingdom (MRC-UK) (2004) *Interim guidelines for research involving human participants in developing societies: ethical guidelines for MRC sponsored studies*

Medical Research Council of Canada, Natural Sciences and Engineering Research Council of Canada and Social Sciences and Humanities Research Council of Canada (1998) *Tri-council policy statement: ethical conduct for research involving humans*

Medical Research Council of South Africa (1993) *Guidelines on ethics for medical research, 3rd edition*

Ministry of Public Health (MOPH) Ethics Committee (Thailand) (1995) *Rule of the medical council on the observance of medical ethics*

National Bioethics Advisory Commission (US) (2001) *Ethical and policy issues in international research: clinical trials in developing countries, Volumes I and II*

National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research (US) (1979) *The Belmont Report*

National Consensus Conference on Bioethics and Health Research (Uganda) (1997) *Guidelines for the conduct of health research involving human subjects in Uganda*

National Health and Medical Research Council of Australia (1991) *Guidelines on ethical matters in aboriginal and Torres Strait Islander health research*

National Health and Medical Research Council of Australia (1999) *National statement on ethical conduct in research involving humans*

National Health Council (Brazil) (1996) *Resolution No. 196/96 on research involving human subjects*

Biomedical and behavioural investigators working in resource-poor settings confront the formidable issue of balancing universally recognized ethical standards for research with local standards and the very real constraints of implementing studies in areas that may be economically compromised, where access to effective medicines or drugs is inadequate or non-existent, and where traditional customs may be in direct conflict with international guidelines for requirements such as informed consent. The disconnection between ideal standards and their application in the real world of structural imperfections and social, political and economic inequities contributes to the moral complexity that surrounds research design and implementation in resource-poor settings globally.

This review considers sociocultural and structural factors that contribute to ethical challenges surrounding research design and informed consent in biomedical and behavioural studies conducted in resource-poor settings. In chapter 2, ethical issues specifically related to research design are examined, including the importance of social and cultural context for collaborative partnerships and capacity building, standard of care and access to benefits associated with research, and independent ERCs. Chapter 3 addresses sociocultural influences on ethical challenges to informed consent. Attention is given to the importance of language and comprehension of information, the communication of risks, and issues associated with the locus of decisional authority to provide consent. Factors surrounding communication, social position and power inequities are examined. The preparation of consent forms and documentation is also considered. Chapter 4 contains ten case vignettes that illustrate ethical challenges in the design and implementation of research and the application of informed consent in resource-poor communities throughout the world. Finally, chapter 5 concludes with recommendations for good practices when conducting international investigations in culturally diverse settings, and suggestions for future research on a broad spectrum of issues relevant to ethical challenges in biomedical and behavioural research in resource-poor settings throughout the world.

## 1.1 Ethical principles in scientific research

Guidelines for ethical conduct in scientific research throughout the world are informed by the following ethical principles: respect for persons; beneficence/nonmaleficence; and distributive justice (Beauchamp & Childress, 2001). The principle of respect for persons emphasizes the importance of individual autonomy and, in the context of participation in scientific research, it refers to the obligation of investigators to honour the wishes of a competent individual regarding their desire to participate in scientific research. A belief that individuals have the capacity to exercise free will—to act voluntarily and with self determination—is an essential aspect of the ethical principle of respect for persons. Requirements for informed consent and confidentiality in the implementation of research are justified by the principle of respect for persons. The principle of respect for persons also suggests that researchers have an obligation to honour the concerns of communities involved in their studies.

The principle of beneficence refers to the obligation of health-care providers and health researchers to act in a way that benefits the health and well-being of participants in scientific investigations; conversely, the principle of nonmaleficence concerns their obligation to do no harm. Taken together, the principles of beneficence and nonmaleficence emphasize the importance of maximizing benefits and minimizing potential harms. The principle of distributive justice is directly linked to issues of equality and fairness in determining who receives the benefits and who bears the burdens of biomedical and behavioural research. Certain populations—ethnic minorities, refugees and immigrants, for example—particularly those in resource-poor environments, may be vulnerable to discrimination, coercion, or other injustices in the implementation of scientific investigations.

Because of its grounding in western analytical philosophy, bioethics has relied primarily on the language of principles and rights (Engelhardt, 1986; Beauchamp & Childress, 2001). This emphasis is reflected in the development of ethical guidelines for research. In recent years, there has been greater attention paid to the importance of cultural context, social practices and social justice and their contribution to the occurrence and resolution of ethical dilemmas (e.g. Weisz, 1990; DeVries & Subedi, 1998; Hoffmaster, 2001; Po-Wah, 2002; Turner, 2003a; Marshall & Koenig, 2004). Approaches to bioethics and its applications in health care and research will be enhanced and strengthened by diverse cultural and philo-

sophical perspectives as the field continues to expand beyond western industrialized nations and broadens its scope to include issues related to context and justice.

## 1.2 Historical background: declarations, guidelines, and policies

The Nuremberg trials following World War II marked an important turning point in public and professional attention to ethical issues associated with human experimentation (Katz, 1972; Annas & Grodin, 1992). These proceedings considered medical experiments conducted by the Nazis on concentration camp prisoners and resulted in the Nuremberg Code (1949) for ethical conduct in scientific research. Voluntary participation and informed consent were viewed as essential requirements for studies involving humans. In 1948, the General Assembly of the United Nations adopted the Universal Declaration of Human Rights. Nearly 20 years later, this document was provided with legal force when, in 1966, the General Assembly adopted the International Covenant on Civil and Political Rights. Article 7 of the Covenant includes language that speaks directly of free and voluntary consent to medical or scientific experimentation.

The World Medical Association's (1964) Declaration of Helsinki reiterated the Nuremberg Code's emphasis on voluntary and informed consent to research as well as other factors important to ethical conduct in scientific investigations involving communities and individuals. The Declaration of Helsinki, revised most recently in 2000, is universally recognized as a foundational guideline for ethical behaviour in scientific research.

The Council of International Organizations of Medical Sciences (CIOMS), in association with the World Health Organization (WHO), has played an important role in establishing international ethical guidelines for biomedical research. CIOMS/WHO began its work on ethics in biomedical research in the late 1970s. A key aim of CIOMS was to provide guidelines for the principles outlined in the Declaration of Helsinki, particularly in relation to the implementation of scientific research in developing countries. In 1982, CIOMS/WHO published the *Proposed international guidelines for biomedical research involving human subjects*. The *International guidelines for biomedical research involving human subjects*, revised in 1993, was endorsed by the WHO Global Advisory Committee on Health Research and the Executive Committee of CIOMS. The most recent revision of the guidelines was published in 2002. The revised text consists of a description of general ethical principles and twenty-one guidelines with commentary; the 1993 revision contained fifteen guidelines. As with the earlier CIOMS guidelines, contributors to the revision were particularly concerned with the application of ethical standards and the establishment of mechanisms for ethical review of human participants in resource-poor settings where local standards for scientific conduct may differ from those in western industrialized nations. In 1991, CIOMS, in collaboration with WHO, prepared a separate document addressing public health and epidemiological research (*International guidelines for ethical review of epidemiological studies*).

In the arena of pharmaceutical research, a collaborative initiative, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was established in 1990 and, in 1996, published *Guidelines on good clinical practice*. This initiative represents drug regulatory authorities of the European Union, the United States (Food and Drug Administration), and Japan (Ministry of Health and Welfare) and representative associations of the pharmaceutical research-based industry in these three regions (European Federation of Pharmaceutical Industries, Japanese Pharmaceutical Manufacturers Association, International Federation of Pharmaceutical Manufacturers Association, and Pharmaceutical Research and Manufacturers of America). Two important goals of the ICH are to improve efficiency in the process of developing and registering medicinal products through the harmonization of technical requirements and to ensure that clinical trial data are mutually acceptable to the joint collaborators. The ICH (1966) guidelines include a common set of technical requirements related to the quality, safety, and efficacy of medicinal products.

National efforts to establish guidelines for ethical conduct in scientific research developed concurrently with the international promulgation of policies and guidelines (e.g. United States Department of Health and Human Services, 1991; Medical Research Council United Kingdom (UK), 1998a; Medical Research

Council of Canada, 1998; Australia: National Health and Medical Research Council, 1999; Uganda: National Consensus Conference, 1997; Indian Council of Medical Research, 2000; Medical Research Council South Africa, 1993). In the United States of America (USA), for example, in 1972, public reports about government research on untreated syphilis among low-income African-American men in Tuskegee, Alabama, called attention to the absence of voluntary participation and the unwillingness of researchers to disclose the availability of a treatment (Jones, 1981). The Department of Health, Education, and Welfare appointed a panel to review the study and, in 1974, the National Research Act was passed which led to the establishment of the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research. The National Commission published the Belmont Report in 1979; this report described basic ethical principles regarding research with human participants (National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research, 1979). Historically, the Belmont Report represents an important contribution to early philosophical considerations regarding research ethics.

Although numerous declarations, proclamations, policies and guidelines for ethical conduct in research have been promulgated, there are inconsistencies between them concerning the use of language and terminology; this has implications for how the guidelines are used by investigators in the field (Emanuel et al., 2000; Macklin, 2004).

### 1.3 Recent developments

In recent years, reports of ethical misconduct surrounding biomedical research in both industrialized and resource-poor countries have resulted in ongoing debates among professionals, policy-makers and the public over a range of issues such as appropriate standards of care, the use of placebos in clinical trials, and obligations to study participants and their communities (e.g. Angell, 1997, 2000; Lurie & Wolfe, 1997; Levine, 1998; Annas, 2001; Macklin, 2001; Shapiro & Meslin, 2001; Varmus & Satcher, 2001; Killen et al., 2002). Challenges associated with informed consent to research conducted in diverse settings throughout the world have also been noted (e.g. National Bioethics Advisory Commission, 2001).

Since the late 1990s, revisions to the Declaration of Helsinki and the CIOMS international guidelines for ethical conduct in biomedical research have been accompanied by lengthy discussions and heated debates over specific language and recommendations. Considerations of local versus universal standards of care were especially problematic in light of the controversy over clinical trials to reduce maternal-fetal transmission of human immunodeficiency virus (HIV) in developing countries (e.g. Bloom, 1998; Levine, 1998; Macklin, 2001, 2004). At this time, other governmental and nongovernmental organizations and agencies were also considering challenges associated with multinational research, particularly investigations conducted in developing countries. For example, in 2000, the Joint United Nations Programme on HIV/AIDS (UNAIDS) published the UNAIDS guidance document entitled *Ethical consideration in HIV preventive vaccine research* (UNAIDS, 2000). In 2001, the Council of Ministers of the European Union and the European Parliament adopted a directive (Directive 2001/20/EC) on clinical trials, binding in 2001 and which had to be implemented by 2004.

In the USA, the National Bioethics Advisory Commission (2001) published a comprehensive two volume report entitled *Ethical and policy issues in international research: clinical trials in developing countries*. This report includes recommendations and an expansive discussion of issues associated with the design and implementation of clinical trials in developing countries. The second volume includes commissioned papers that provide detailed background information and results of international investigations on informed consent and ERCs.

The following year, the Nuffield Council on Bioethics (2002) published *The ethics of research related to healthcare in developing countries* (see also updated report, Nuffield Council on Bioethics, 2005). This report represents the deliberations of an international working group charged with considering health care-related research involving populations and patients in developing countries. As with the National Bioethics Advisory Commission report, the Nuffield Council on Bioethics paid special attention to issues that arise when research is sponsored by an institution in a developed country and carried out in a resource-limited setting. The report includes a review of the economic context of health care, high-

lighting health disparities between countries and research priorities. Social and cultural issues surrounding illness, health-care delivery and research are addressed. Recommendations and guidelines are provided for informed consent, standards of care, ethical review of research, and the obligations of researchers when studies end.

In recent years, there have been increasing efforts to address ethical issues in international research through educational programmes and policy and infrastructure development on the part of governmental and non-profit agencies. The Department for Ethics, Trade, Human Rights and Health Law of WHO actively promotes programme development on a broad range of ethical issues in biomedicine and science in clinical and research settings worldwide (WHO 2004). The UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) plays a major role in promoting ethics in research, including publications on topics such as guidelines for research ethics boards and data and safety monitoring boards. The capacity-building activities of the TDR Programme led to the development of The Strategic Initiative for Developing Capacity in Ethical Review (SIDCER), a network of regional fora for ethical review committees and health researchers globally. The Fogarty International Center (FIC) at the National Institutes of Health in the USA promotes ethics initiatives through educational programmes, research and capacity building in resource-limited countries. The FIC is one of the sponsors of the Global Forum on Bioethics, now in its sixth year of existence, whose aim is to further international debate on ethical issues in biomedical research.

Based in the UK, the Wellcome Trust<sup>1</sup> promotes attention to ethical considerations in international research through their collaborative sponsorship of conferences focused on ethical concerns in scientific research in resource-poor settings and through a grants award programme to fund investigations on the ethics of biomedical research in developing countries. Similarly, the Nuffield Council on Bioethics<sup>2</sup>, supported by the Nuffield Foundation, the Wellcome Trust and the UK Medical Research Council, has contributed significantly to policy development in the area of international research ethics through conferences and publications.

Taken together, initiatives such as these illustrate the serious consideration now being given to the complex and wide-ranging issues surrounding the design and implementation of multinational research, particularly investigations conducted in developing countries. Some critics might claim that efforts to address ethical quandaries in international research simply result in the promulgation and globalization of a western-based orientation to ethical principles and their application to scientific studies. This perspective denies the historical importance of a broad-based, international movement on the part of governmental and non-governmental agencies, policy-makers, academicians, and the general public to increase efforts to improve research practices in resource-poor settings.

Current debates over ethical issues relevant to the practice of international research will continue. Existing health disparities between resource-rich and resource-poor countries, combined with the substantial inequities in access to health-related resources, require engaged and thoughtful dialogue about the ethical implications surrounding the application of ethical guidelines and standards of research practice. Fundamental questions remain. How should we resolve cultural differences about the underlying foundations and assumptions of ethical guidelines for research? What role should researchers have in diminishing the economic and health disparities that divide the North and South, and contribute to some of the key ethical dilemmas in conducting studies in resource-poor and marginalized communities? The issues are morally complex and embedded in social history, cultural context, and the global political economy.

In this report, attention is given to the social and cultural contexts influencing ethical issues that arise in the design of biomedical and behavioural research and in approaches to informed consent. Negotiating consensus about research ethics across international boundaries is a complicated process that is fraught with ideological and practical conflicts. However, attention to cultural context and social justice in relation to the conduct of international research in poor communities has important implications for revisiting and transforming existing ethical guidelines and their application to research practices (e.g. National Bioethics Advisory Commission, 2001; Nuffield Council on Bioethics, 2002, 2005; Macklin, 2004).

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<sup>1</sup> The Wellcome Trust: <http://www.wellcome.ac.uk/> (accessed July 17 2004)

<sup>2</sup> Nuffield Council on Bioethics: <http://www.nuffieldbioethics.org> (accessed July 17 2004)



## 2. ETHICAL CHALLENGES IN RESEARCH DESIGN

Ethical challenges associated with the design of biomedical and behavioural studies are embedded in sociocultural, economic and political contexts at all levels—local, national, and global. Recognition of the importance of conforming to international ethical guidelines for biomedical and behavioural research suggests that there is consensus regarding the acceptability of “universal” ethical principles governing scientific investigations. However, the sociocultural environment and structural capabilities of institutions and communities differ significantly in diverse settings where research is implemented. In recent years, there has been increased attention to the need to respond appropriately to the globalization of biomedical and social behavioural research, particularly in resource-poor environments (e.g. Macklin, 2004). Building on their earlier framework for ethical conduct in scientific investigations (Emanuel et al., 2000), Emanuel and colleagues (Emanuel et al., 2004:931) have outlined eight ethical principles and practical benchmarks to guide multinational research: (1) collaborative partnership; (2) social value; (3) scientific integrity; (4) fair selection of study populations; (5) favourable risk/benefit ratio; (6) independent ethical review of protocols; (7) informed consent; and (8) respect for participants and communities. The following sections explore the articulation of these principles and benchmarks in research design with attention to: first, cultural context, collaborative partnerships and capacity building; second, standards of care and access to benefits derived from research initiatives; and third, independent review of research protocols.

### 2.1 Cultural context

Guidelines such as those promulgated by the Helsinki Declaration (World Medical Association, 2002), CIOMS (2002), the Nuffield Council on Bioethics (2002; 2005) and the National Bioethics Advisory Commission (2001) reinforce a commitment to transcending cross-cultural differences by mandating that the same standards be applied to research participants from both resource-poor and industrialized countries (e.g. Brody, 1998; Sugarman et al., 1998; Macklin, 2004). Research participants in any cultural setting, for example, should provide individual voluntary consent, and studies that could not be conducted in an industrialized country should not be implemented in a developing country. Nevertheless, the problem of balancing universal and local standards for ethical conduct in biomedical or behavioural research is challenging when investigators confront the very practical constraints of implementing a study in areas where traditional customs may be in conflict with international guidelines, in impoverished nations that bear a disproportionate burden of disease morbidity and mortality, and in areas that lack adequate health resources.

The application of general ethical principles underlying guidelines for research is difficult to accomplish without knowledge of the cultural context within which a study will take place. Anthropologists have described culture as a symbolic system representing ideas, values, cosmology, morality, and aesthetics shared by individuals and groups (e.g. Kuper, 1999:227). Cultural symbols, beliefs, and values are not socially, historically, or geographically static; culture is inherently dynamic and porous, particularly in a world of globalization and instantaneous communication (Appadurai, 1996). Thus, cultural attributes are responsive to contemporary social and political realities.

Despite the fluidity of cultural beliefs and the rapidity of culture change in light of global social influences on communities everywhere, very real differences persist. Early in the development of bioethics, Fox & Swazey (1984) called attention to the importance of social context for medical morality and, increasingly, bioethicists and others have recognized the extent and significance of cultural difference in relation to morality in science and biomedicine—and by extension, scientific research (e.g. Marshall & Koenig, 2004, 2004; Kleinman, 1995; Brandt & Rozin, 1997, 1999; Devries & Subedi, 1998; Hoffmaster, 2001; Po-Wah, 2002; Peppin & Cherry, 2003; Turner, 2003a; Devries, 2004). Moreover, the robust body of work by social scientists highlights the profound variability of cultural beliefs and their

impact, not only on health behaviour, but on beliefs about morality across cultures (e.g. Geertz, 1973, 1983; Lock & Gordon, 1988; Scheper-Hughes, 1992; Good, 1994; Shweder et al., 1997; Lock, 2002).

In her book *Against relativism*, Macklin (1999:4) articulates the dominant western ethical perspective on cultural differences, calling attention to the basic issue of discerning between “*fact*” and “*value*”—between “*what is*” and “*what ought to be*”:

“[E]ven if we grant that cultural relativity is an accurate description of the world’s diversity, whether anything follows for normative ethics is an entirely different question. Do the facts of cultural relativity compel the conclusion that what is right or wrong can be determined only by the beliefs and practices within a particular culture or subculture?”

This view of “anti-relativism” is anchored in the notion that certain ethical principles reflect a common morality and are applicable cross-culturally (Beauchamp, 2003; Veatch, 2003). Commentators suggest that values and principles that are universally shared can be differentiated from particular moral norms that are not shared by individuals or populations (e.g. Beauchamp, 2003:259). However, as Marshall & Koenig (2004) and Turner (2003b) point out, consensus about a common morality dissolves when there are efforts to translate general principles into policies or practical guidelines.

The complex realities experienced by people everywhere reveal nuanced and multiple renderings of morality, suffering and health in local social contexts (Kleinman et al., 1997). In some settings, cultural beliefs regarding the cause and treatment of disease may differ radically from western views about underlying disease etiology (Tambiah, 1990; Nichter, 1992; Sargent & Johnson, 1996). Sickness or death may be attributed to witchcraft or sorcery rather than biomedical explanations evoking infectious agents, genetic predispositions, or weak immune systems—explanations central to the western biomedical model of disease. Suffering and illness are interpreted through a cultural lens informed by social context, emotional awareness, physical sensations, and past experience. Moreover, how individuals respond to an episode of illness will be constrained by the health resources and practitioners available to treat them. In many settings, traditional healers and biomedically trained professionals are used simultaneously or, alternatively, individuals may apply a strategy in which home remedies are applied first, followed by consultations with traditional healers, and finally, visits to biomedical practitioners.

A reluctance to discuss death, the possibility of death, or potential harms surrounding medical interventions is shared by individuals and communities from diverse cultural backgrounds. Additionally, in western industrialized settings, telling the truth to patients—and to individuals considering participating in a research project—is expected (Pellegrino, 1992; Pang, 1999). However, beliefs about truth telling, disclosure of information, and the importance of frank and open communication are not universally shared or valued. Moreover, the western emphasis placed on personal autonomy regarding health-care decisions and research participation is not consistent with decision-making patterns that stress the importance of involving family members, religious leaders, or community elders when decisions must be made.

The nature and scope of diverse cultural perspectives on health and illness, and beliefs about disease etiology, treatment efficacy, truth telling, and decisional authority concerning health care have serious implications for the application of ethical guidelines for scientific research. An alternative paradigm to a rigid application of ethical standards in research involving human subjects is proposed by King, Henderson & Stein (1999) who suggest focusing on social relationships in addition to ethical principles. From this perspective, moral principles governing research are meaningful only in social context: “The circumstances do not determine *whether* any of these ‘Western’ moral concepts applies, but *how*” (King et al., 1999:213).

When investigators show respect for cultural context in host communities, they are embracing principles underlying guidelines and recommendations for ethical conduct in the design and implementation of research. Identifying a study population and establishing methods for recruitment, for example, necessarily requires attention to local socioeconomic conditions and cultural beliefs. Even when a designated population is viewed as appropriate for achieving scientific aims, investigators must consider potential risks and harms for study participants in their local communities. The notion of vulnerability

has been applied to groups affected by a broad range of conditions. Because of this, some critics charge that the concept has lost its force and specificity in the context of research with human participants (Levine et al., 2004). Nevertheless, determining fair selection of subjects and assessing risks associated with study participation demand that investigators identify sources of potential exploitation or coercion based upon, for example, cultural beliefs about gender roles, beliefs about illness and disease that contribute to the stigmatization of individuals, and marginalized social status due to poverty, religion, political views, sexual practices, or involvement in illegal activities.

## **2.2 Health disparities**

In addition to cultural beliefs and traditions, the quality of life and the experience of suffering or health for individuals and populations worldwide is profoundly influenced by social, political, and economic factors. Stark inequalities in health care are found throughout the world. Individuals in industrialized countries have access to excellent public health resources and state-of-the-art medical therapies and vaccines. In sharp contrast, individuals and communities in resource-poor nations are burdened with high rates of infectious diseases, inadequate public health conditions, and insufficient or inaccessible medical care. Less than 10% of global expenditures for health research by private and public sectors are devoted to addressing 90% of the world's health problems (Global Forum for Health Research, 2000). This dramatic calculation—referred to as the “10/90 gap”—profoundly affects the health of developing nations.

Bioethicists and others have begun to consider carefully the range and scope of broader structural issues contributing to global population health, including socioeconomic and political factors influencing the disproportionate burden of disease throughout the world (e.g. Mann et al., 1999; Farmer & Gastineau, 2004; Gostin, 2004; Kass, 2004). Social justice is a key consideration. Benatar, Daar & Singer (2003:108) believe that bioethics has the potential to contribute significantly to global health reform through five transformational approaches: “...developing a global state of mind; promoting long-term self-interest; striking a balance between optimism and pessimism about globalization and solidarity; strengthening capacity; and enhancing the production of global public goods for health.” In their substantive analysis of criteria for a globally relevant bioethics, Benatar and colleagues (2003) stress the important relationship between structural factors that impact population health and international politics that contribute to and, in some cases, reinforce inequities. Farmer (1997, 2003), an anthropologist and physician dedicated to human rights issues in international health, is critical of any attempt to excuse the powerful ways in which structural forces influence health and human suffering, particularly when efforts are made to invoke the “culture argument” to rationalize disparities.

## **2.3 Strengthening the commitment to ethical conduct in research design**

In this section, three activities particularly relevant to designing and implementing ethically responsible research in resource-poor settings are addressed: (1) developing collaborative partnerships; (2) strengthening and building capacity; and (3) independent ethical review of protocols.

### *2.3.1 Collaborative partnerships in research*

Recognizing the need for local expertise in developing countries, the Nuffield Council on Bioethics (2002; 2005) recommends that research sponsors promote partnerships between researchers from developed and less developed countries. The National Bioethics Advisory Commission (2001:30) suggests that, “researchers and sponsors should involve representatives of the community of potential participants throughout the design and implementation of research projects.” UNAIDS (2000) now provides guidance for investigators noting that community representatives should be involved early in the development of a study to ensure the ethical and scientific quality of proposed research and its relevance to and acceptance by the community.

Collaborative partnerships are identified as a key component in the ethical framework for multinational clinical research developed by Emanuel and associates (2004:931); respecting a “community’s values, culture, traditions, and social practices” is viewed as an essential aspect in building effective partnerships. Ideally, collaborative relationships begin long before the project is initiated through extensive interaction with local investigators and community members about the study goals and strategies to ensure its successful completion. Community involvement should be an ongoing process in which the community is kept aware of research activities and findings (Marshall & Rotimi, 2001).

Ensuring that individuals and communities receive benefits from their participation in a study requires not just considerations for the provision of medicines or other interventions that are proven to be effective, but also attention to strategies for sharing financial gains from the research with communities. In the arena of intellectual property rights, for example, conflicts over the products and patents resulting from genetic research in indigenous populations present thorny ethical problems. The inclusion of information about intellectual property rights on an informed consent document cannot promise how benefits will accrue to populations, nor do consent forms necessarily address the potential for group harms resulting from research with indigenous populations. Emphasizing procedural solutions may represent an unsatisfactory response for populations whose beliefs about processes of community decision-making concerning scientific studies and intellectual property rights may be very different from those of the researchers (Brown, 2003).

Additionally, investigators must be sensitive to how community power and authority are expressed in diverse cultural environments. Adebamowo (this volume, Case 4) describes the impact of local community dynamics on conducting scientific research in sub-Saharan Africa. Researchers involved in an international collaborative project focused on genetics inadvertently risked interfering with the local power structure through the establishment of a community advisory board. Attempts to establish mechanisms for sharing the financial rewards associated with research depend upon a clear understanding of both formal and informal patterns of community leadership.

### 2.3.2 *Capacity building*

Capacity building in resource-poor settings helps ensure the sustainability of collaborative partnerships and the interventions found to be effective in research (e.g. Jinadu, 1997; Crawley & Himmich, 2000; Kovacic & Laaser, 2001; Nchinda, 2002, 2003; Lo & Bayer, 2003; Chandiwana & Ornbjerg, 2003; Lavery, 2004). Capacity building may include a range of activities such as hiring and training research personnel, providing technical resources or medical care, and strengthening health infrastructures. In his extensive work on the HIV epidemic, for example, Farmer and colleagues at Partners in Health rejected the widely-held belief that only strategies for the prevention—but not treatment—of acquired immunodeficiency syndrome (AIDS) should be used in resource-poor countries, and that some cultural beliefs inevitably lead to non-compliance with complex medical regimens. They successfully used anti-AIDS drugs in Haiti and shattered the rationalization that therapy would not be cost-effective in certain cultural groups (Mukherjee, 2003). Their systematic efforts included transforming some of the underlying structural problems by revitalizing the public health infrastructure, hiring and training health professionals for active case finding, and increasing wages to encourage staff to remain working in the rural area.

Another important area for capacity building concerns strengthening and reinforcing the ability of research ethics review committees (ERCs) and institutional review boards (IRBs) to conduct independent review of protocols. Educational programmes for committee members—in resource-poor and in industrialized countries—should concentrate on both the importance of understanding ethical principles and their articulation in guidelines for research and the need to recognize the influence of local social contexts on the implementation of research and the application of ethics guidelines.

Respecting the cultural beliefs and practices of communities participating in research and simultaneously working towards diminishing existing health disparities through collaborative partnerships and

capacity building is a major challenge for investigators. The myriad and complex problems require what Benatar (2000:564) calls "...the development of international strategic alliances" between professionals and communities representing diverse backgrounds and expertise in both public and private sectors.

### 2.3.3 *Independent ethical review of protocols*

Throughout the world, independent Ethical Review Committees (ERCs) have been established to provide oversight and approval for proposals to conduct biomedical and behavioural research. There is general agreement about the nature and scope of responsibilities for ERCs. Reviews of scientific protocols may be conducted by committees or boards established by local institutions or constituted at the regional, national or, in some cases, international level. The primary aim of ERCs is to ensure the protection of human participants by safeguarding their rights and determining that the risks associated with participation in the study do not endanger the safety of individuals and are reasonable in relation to the anticipated benefits.

National and international guidelines emphasize that ERCs are responsible for addressing the following issues in their deliberations of research protocols:

- scientific integrity, a sound research design;
- consideration of risks/benefits;
- equality in treatment of subjects;
- monitoring of data collection;
- informed consent;
- documentation of informed consent;
- protection of privacy and confidentiality; and
- a statement indicating that participation in the research is voluntary and that withdrawing from the study will not result in harm or penalty (e.g. United States Department of Health and Human Services Office for Protection from Research Risks [now OHRP], 1991; Medical Research Council UK, 1998a; Indian Council of Medical Research, 2000; WHO, 2000; CIOMS, 2002; Nuffield Council on Bioethics, 2002).

Guidelines recommend that ERCs should be comprised of individuals representing diverse professional backgrounds including, for example, biomedical and behavioural scientists, physicians, lawyers, nurses, and ethicists or members of the clergy. Additionally, ERCs should include members of the public who are able to represent the "community" being served by the research.

A perennial issue for ERCs concerns the requirement to differentiate and adequately address the need for scientific and ethical assessments of proposed investigations. The CIOMS guidelines (2002) indicate that normally committees consider both scientific and ethical review of research; appropriate scientific review must be arranged if the ethics committee is not able to perform this function. The Nuffield Council on Bioethics (2002) outlines three levels of assessment for research: (1) relevance to priorities in health care within the country(ies); (2) scientific validity; and (3) ethical acceptability. They acknowledge that it may not be possible to separate the science and ethics review of proposals but recommend that, when possible, these two forms of review should be kept separate which may, in some cases, require the establishment of two committees. Similarly, in their recent report on the protection of research participants, the Institute of Medicine (2003) of the National Academy of Science in the USA, recommended that systematic assessment of the scientific merits of a proposal—and conflicts of interest—should be conducted before the ethics review and that the ERC should be provided with summaries for their ethics deliberations.

IRBs and ERCs have had a profound impact on the regulation of research with human subjects (Faden & Beauchamp, 1986; Levine, 1986). While there is consensus about the general purpose of IRBs and

ERCs, significant challenges remain in the application of the review process in both industrialized and developing countries. Challenges may be exacerbated in resource-poor environments. For example, there may be structural impediments that exist within institutions that make it difficult to fulfil international ethical regulatory requirements, including lack of resources, insufficient training among ERC members, and inadequate infrastructures. Effective ethical review of scientific protocols assumes that appropriate individuals are available and able to conduct reviews, that people have a shared understanding about the need for ethical review of protocols and the responsibilities associated with it, and that institutions have the technological resources to implement reviews including funds for photocopying materials and support staff for managing and tracking protocols. However, in many developing countries where research is conducted, research ethics committees may be non-existent or unable to perform reviews adequately because of insufficient resources or the absence of trained professionals.

Hyder and colleagues (2004) surveyed 670 health researchers in developing countries regarding the role of IRBs in ensuring the adequacy of ethical standards. They found that 44% of the respondents said their research was not reviewed by an IRB from the developing country or ministry of health; one third of these studies were funded by organizations in the USA. The results of their study also indicate that IRBs in the USA were significantly more likely to raise questions about issues such as the need for consent forms in the local language and the protection of confidentiality than were IRBs in the host country.

Macpherson (2001a, 2001b) describes the uncertainties that arose in the establishment of a research ethics committee in Grenada. Questions centred on which guidelines and what procedures to follow and the appointment and training of members. Macpherson (2001b) notes that international guidelines do not address the relationship of the IRBs to governments that have no mandate for them. However, Macpherson's (2001b) description of the Grenada experience demonstrates that it is possible for IRBs in developing countries to adhere to international standards. She argues that there is a great need for educational programmes not just to enhance the capacity of IRBs, but also to ensure that leaders of developing countries are knowledgeable about the value of international research guidelines for their nations.

National and international guidelines outline specific recommendations for externally sponsored research conducted in developing countries. Ethical guidelines underscore the importance of independent ethical review in both the sponsor's country (or countries) and the country(ies) where the research will be implemented. Externally sponsored research conducted in resource-poor settings presents a number of ethical challenges. One difficulty concerns the duties and obligations for research oversight when different ethics review boards are involved. For example, in their description of a clinical trial for HIV/AIDS in China, Henderson & Yu (this volume, Case 1) call attention to the confusion surrounding the roles and responsibilities of the separate IRBs charged to review studies in multisite international collaborations. In his consideration of IRBs in developing countries, Pape (2001:547) recommends that, "...the primary responsibility of local and national IRBs should be clearly determined," and that the IRBs involved should share responsibilities in order to maximize benefits for study volunteers.

Often, IRBs in sponsoring institutions may not be familiar with the social and cultural issues that have an impact on ethical conduct of studies in host countries (White, 1999; Eckenwiler, 2001; Beyrer & Kass, 2002; London, 2002; Cola, 2003). National and international guidelines stress the important contribution that IRBs in the host country make to assessments of the relevance of the study for local populations, the cultural appropriateness of the research design and informed consent procedures, and risks associated with study implementation for participants and communities (e.g. United States Department of Health and Human Services, 1991; Medical Research Council UK, 1998b; Indian Council of Medical Research, 2000; National Bioethics Advisory Commission, 2001; CIOMS, 2002; Nuffield Council on Bioethics, 2002, 2005). In her proposal for addressing guidelines for IRB review of international collaborative research, White (1999:9) uses the term "negotiated ethic" (Baker, 1998) to refer to a process that acknowledges fundamental ethical standards and sociocultural values of both the sponsoring and host countries. However, White (1999) believes that the IRB representing the sponsor of the study should have the "last word" on approval of a protocol because sponsoring researchers are ultimately responsible to their funders and institutions for compliance with federal and institutional ethical stan-

dards. Nevertheless, she is in agreement with other scholars and critics in acknowledging that host IRBs should be able to modify western standards to accommodate the local context and interests of the study participants. Thorny questions remain concerning whose authority “trumps” in resolving disagreements over the application or interpretation of guidelines when they occur.

In 1998, the United States Office of Protection from Research Risks (the precursor to OHRP) issued a guidance document stating that IRBs must ensure that they have sufficient knowledge of the local context to assess adequately the risks of study participation for individuals and communities. Cola (2003) describes the successful implementation of what is called “local context review” of protocols for the IRB at the University Hospitals of Cleveland (UHC), Ohio, in the USA; UHC is the primary affiliate of Case Western Reserve University. In this case, individuals who are from the country or specific area where a study will take place, or someone very knowledgeable about that particular cultural environment, is enlisted as a consultant to review the protocol. Local context reviewers offer advice on simplification of consent forms and on approaches to minimize any negative social effects of participation in the research study. Cola (2003) points out that local context review does not replace host-country IRB review, but supplements information that may not be available from the IRB in the host country.

International funding agencies exert considerable power over the ethical review of biomedical research. Scientific research represents an international economic force; involvement in research means access to financial and technological resources, educational training, and other direct or indirect forms of capacity building for host institutions and for individuals and the communities and nations where they live (Marshall & Koenig, 2004). In some settings, ERCs in developing countries may feel pressured to approve protocols in order to access the professional and financial benefits associated with the implementation of a research project. In other settings, ethical review boards may not be able to function effectively because they lack independence or authority or because they are viewed simply as a formality (e.g. National Bioethics Advisory Commission, 2001; Nuffield Council on Bioethics, 2002). In the cases described by Raja (Case 9, this volume), members of the ethics committee questioned the researchers’ obligations to provide medical care for participants involved in the study and their obligations for capacity building for health-care infrastructures at study sites. The researchers expressed frustration with the committees’ objections, and in one case, the researchers from the sponsoring institution in an industrialized country withdrew their protocol and moved the study to another location where it was “rubber-stamped” and approved without question by the local review board.

Another challenge concerns the selection of committee members. Although committees are required to include representatives from non-scientific fields and from the community, most are dominated by scientists who are responsible for reviewing the research protocols of colleagues and friends. Questions regarding professional competence arise in determining who is qualified to judge the professional merit of protocols. Professional bias may be an obstacle to objectivity regarding determination of harm to research subjects. The strong value placed on promoting scientific research among most committee members may outweigh the concerns of a community representative. Moreover, lay members may experience psychological pressure to reach consensus and therefore they may be inclined to accept the arguments of a “professional.” Additionally, the community representative may not understand adequately the risks associated with participation or whose interests are served by research agendas.

One of the difficulties associated with ethical review of research protocols is the variability and inconsistent interpretations of guidelines on the part of individual ERCs. Guidelines outline general criteria and recommendations, but these are applied at the discretion of local members. Judgments about what constitutes unreasonable risks, appropriate standards of care, or approaches to informed consent may differ significantly between local IRBs or ERCs, depending upon the preferences, priorities and experience of members.

MacQueen and colleagues (2004:55), for example, describe an approach to informed consent that would balance United States requirements for documentation and the need to protect confidentiality of individuals involved in a study of HIV prevention in an illiterate population. One member of the research team would describe the study, obtain the thumbprint signifying consent from a participant,

and then sign the form indicating that the individual had appropriately consented. Another team member would then ask a series of questions to verify understanding of the essential elements of consent and afterwards sign the form as a second witness to the consent process. However, this process differed from the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH], 1996) GCP-based standards for research which require the simultaneous witnessing by two individuals. MacQueen and associates (2004) report that negotiating changes to the ICH standards has proven difficult and often are ineffective.

The vulnerability of research populations globally raises important questions for IRBs and ERCs (Beyrer & Kass, 2002; London, 2002; Levine et al., 2004). In the context of international research, Levine and colleagues (Levine et al., 2004) argue that the concept of “vulnerable populations” has lost its force because so many groups have been labelled as susceptible to exploitation or harm; they believe that particular individuals and communities require ongoing protections that are established in laws or regulations, and that, additionally, attention must be paid to ethical challenges associated with the research design and the environment where the study will take place. Beyrer & Kass (2002) call attention to the issue of human rights and the ethical review process, noting that every aspect of the research ethics review—balancing risks and benefits, assuring the rights of individuals and communities, and the fair selection of research participants—is affected by the political and human rights context within which the study is conducted. Beyrer & Kass (2002) argue that research viewed as low risk in one setting may become high risk in another, particularly under conditions where a breach of confidentiality could result in abuse of study participants or where results might be used to disempower individuals or communities. Beyrer & Kass (2002) recommend that researchers contact human rights organizations or someone knowledgeable about the local or national politics to determine whether it is feasible to conduct a study in that area.

In his examination of ethical oversight for public health research, London (2002) asks whether IRBs can make a difference in developing countries. Currently, IRBs and ERCs focus considerable attention on informed consent documents rather than on other aspects of research design (Macpherson, 1999; White, 1999; Kass & Hyder, 2001; Sugarman et al., 2001; Kass et al., 2003). London questions whether it is the responsibility of ERCs to address what Benatar (2002) has called “macro issues” that contribute to health disparities and the disproportionate disease burden on populations in resource-poor nations. Although London recognizes the profound limitations of ethics committees, he believes that a narrow view of their responsibilities loses sight of the broader issues and challenges that face public health research. Moreover, London (2002) argues that vulnerable communities and countries will remain in need of protection until they are empowered with the agency to initiate and manage their own health care effectively.

Capacity building for IRBs and ERCs, and for the researchers and communities served by them, is an essential aspect of any initiative to strengthen the ethical review of scientific investigations in resource-poor environments (Crawley & Himmich, 2000; Karbwang et al., 2002; Ahmad 2003; Fitzgerald et al., 2003). Governmental and non-profit-making agencies have begun, in recent years, to provide extensive support and training on ethical guidelines for international research and the establishment of IRBs. The UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), for example, has launched a number of initiatives in collaboration with the Office of Human Research Protections (USA), the Food and Drug Administration (USA), the European Forum for Good Clinical Practice, and the International Federation of Pharmaceutical Manufacturers Associations. Illustrating their commitment to capacity building, TDR/WHO has published operational guidelines for ethics committees that review biomedical research (2000). Additionally, this global partnership has organized the Strategic Initiative in Developing Capacity in Ethical Review (SIDCER, 2004). The aim of SIDCER is to promote best practices in ethical review by strengthening regional and in-country capacity through educational forums and networking.

Efforts to promote capacity building for ethical review of biomedical and behavioural research in developing countries are likely to continue given the increased public and professional attention to the complex ethical issues surrounding multinational biomedical and behavioural investigations. However, it is



important to recognize that challenges surrounding capacity building, training, and resource allocation for ERCs are concerns in industrialized nations, not just in resource-poor countries. Capacity building for IRBs in industrialized settings should emphasize being cognizant of cultural differences when reviewing collaborative research. Additionally, in some international settings, there is always the danger of reproducing the same problems that confront IRBs in industrialized countries.

## 2.4 Standard of care and access to fair benefits

Perhaps the most contentious debates in recent years have been over appropriate standards of care in clinical trials conducted in developing countries. In the late 1990s, controversy surrounding trials testing the efficacy of short-term and less expensive alternatives to standard antiretroviral therapy for reducing perinatal transmission of HIV in developing countries called attention to inconsistent interpretations and applications of national and international ethical guidelines (Angell, 1997; Lurie & Wolfe, 1997; Varmus & Satcher, 1997; Bloom, 1998; Levine 1998; Lie, 1998; Luna, 2001; Macklin, 2001; Killen et al., 2002). These trials, sponsored by the National Institutes of Health and the Centers for Disease Control in the USA and conducted in south-east Asia and Africa, raised questions about the comparison of experimental treatments with locally available therapies or the best proven therapies worldwide. The primary issue in the standard-of-care debate centres on the possibility of exploitation, particularly for populations in resource-poor settings. While there is consensus that research participants should receive the best therapy available worldwide, some commentators believe that this requirement might be an obstacle to conducting important research that may improve health conditions, particularly in developing countries (Wendler et al., 2004).

Pragmatists might argue that the urgency of the problems being researched—such as methods to control the spread of HIV—combined with the lack of existing or sustainable alternatives to universally accepted methods—justifies and requires the use of less than the worldwide best treatments in clinical trials. At the opposite end of this polarized debate are those who argue for adherence to state-of-the-art therapeutic interventions, regardless of local standards and the sustainability of treatments (e.g. Angell, 1997, 2000; Lurie & Wolf, 1997; Rothman, 2000; Annas, 2001; Shapiro & Meslin, 2001). There are, however, wide disparities in existing health resources and local standards of care between industrialized and developing countries, and between institutions within countries. Currently, in many resource-poor environments, universal standards cannot be sustained. Moreover, global social and economic conditions influence the availability and distribution of resources for health care in all nations.

The specific terminology addressing standard of care for clinical trials varies in international guidelines. The Nuffield Council on Bioethics (2002) refers to a “universal standard” as “the best treatment available anywhere in the world.” The revised CIOMS (2002) guidelines refer to an “established effective intervention” as an ethical comparison in clinical trials. Paragraph 29 of the Declaration of Helsinki (World Medical Association, 2000) has been the focus of considerable debate: “The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods.”

There is now general agreement among all international guidelines that placebo-controlled trials are justified when a proven treatment does not exist (e.g. Nuffield Council on Bioethics, 2002, 2005; CIOMS, 2002; see Macklin, 2004 for a full discussion). A note of clarification for paragraph 29 regarding the use of placebos was incorporated in the 2002 revision of the Helsinki Declaration (World Medical Association, 2002): “[A] placebo-controlled trial may be ethically acceptable, even if proven therapy is available...where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic methods.” However, Levine, Carpenter & Appelbaum (2003) suggest that critics of the language used in the 2000 revision of the Helsinki Declaration may now be concerned that the recent clarification could be interpreted as being overly permissive. Levine and colleagues (2003) suggest that the CIOMS revised guidelines (2002) provide more specific guidance concerning the use of placebos:

An exception to the general rule (requiring established effective treatment as the control condition) is applicable in some studies designed to develop a therapeutic...intervention for use in a country...in which an established effective intervention is not available and unlikely in the foreseeable future to become available, usually for economic or logistic reasons. The purpose of such a study is to make available to the population of the country...an effective alternative to an established effective intervention that is locally unavailable... Also, the scientific and ethical review committees must be satisfied that the established effective interventions cannot be used as comparator because its use would not yield scientifically reliable results that would be relevant to the health needs of the study population.

In their critical analysis of the standard-of-care debate, Wendler and colleagues (2004) outline a framework that specifies conditions under which it would be acceptable for participants to receive less than a universally accepted "best method". They argue that the default position of IRBs should be a requirement for "worldwide best" methods, but that IRBs should be willing to grant exceptions for studies that meet the following four conditions. The first condition, scientific necessity, refers to the need for investigators to use less than universally recognized best methods in order to answer the scientific question addressed in the clinical trial. Using this framework, the controversial HIV vertical transmission trials investigating short course alternatives to the 076 regimen (the best method for preventing maternal-fetal transmission) represents a case where exemption to the "best method" approach could be justified because of scientific necessity.

The second condition proposed by Wendler and colleagues (2004) considers the relevance of the study for the host community and emphasizes that the proposed research will help address important health concerns for communities participating in studies. The third condition considers the need for the clinical trial to produce a fair level of benefit for the communities participating in the study. The fourth condition outlined in their framework refers to subject and host community nonmaleficence; research participants and their communities must not be "prospectively worse off" than they would if the trial were not conducted.

#### 2.4.1 *Access to fair benefits*

An issue directly related to standard of care in clinical trials concerns the obligations of researchers to host communities when studies are completed. Investigators, policy-makers, and participating communities are challenged by the myriad complications that arise in considerations of post-trial benefits. There is consensus that trial participants should benefit from treatments proven to be successful, but there is less clarity on how this should be negotiated with host communities and what strategies should be considered for implementing post-trial benefits. Particularly challenging are obstacles associated with inadequate health infrastructures in resource-poor environments and the ability to secure funding for post-trial interventions and drugs.

Guidelines provide varying degrees of specificity regarding obligations to ensure access to treatments proven to be successful in research and to whom they should be provided. The revised CIOMS (2002) guidelines, for example, call attention to the need for "reasonable availability" of post-trial therapies:

[A]ccordingly, the proposed investigational intervention must be responsive to the health needs of the population from which the research subjects are recruited and there must be assurance that, if it proves to be safe and effective, it will be made reasonably available to that population.

National guidelines in countries such as South Africa (Medical Research Council of South Africa, 1993) and Uganda (National Consensus Conference, 1997) frame the issue of post-trial benefits in general terms. Other guidelines are more expansive in providing direction. For example, UNAIDS (2000) states explicitly that, "Any HIV preventive vaccine demonstrated to be safe and effective...should be made available as soon as possible to all participants in which it was tested, as well as to other populations at high risk of HIV infection. Plans should be developed at the initial stages of HIV vaccine development to ensure such availability."

CIOMS (2002), in guideline 10 and its commentary, emphasizes the role of the sponsoring agency in determining mechanisms to provide post-trial drugs or vaccines, "As a general rule, the sponsoring agency should agree in advance of the research that any product developed through such research will be made reasonably available to the inhabitants of the host community or country at the completion of successful testing." In 2004, the World Medical Association added a point of clarification to paragraph 30 of the Declaration of Helsinki that recognizes the importance of researchers, sponsors, and IRBs in determining post-trial benefits:

The WMA hereby reaffirms its position 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.

Similarly, the Nuffield Council on Bioethics (2002, 2005) recommends that post-trial benefits should be considered by researchers, sponsors, national health-care authorities, international agencies and research ethics committees before investigations involving tests of new interventions begin. The Nuffield Council on Bioethics (2002) also endorsed the National Bioethics Advisory Commission's (2001) recommendation that researchers must justify the absence of arrangements for securing post-trial access to effective interventions to ethics committees.

Recently, scholars from eight African and three Western nations outlined a detailed framework for considering "fair benefits" for study populations to ensure that participants and their communities are not subject to exploitation (The Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries, 2004). This framework includes three broad principles with fourteen specific benchmarks (The Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries, 2004:23). The first principle, "Fair Benefits," specifies benefits that should be assessed for both participants and the population during the research and after the study is completed. Included among benefits at the completion of the study are: (a) availability of interventions proven to be effective; (b) capacity development through improvements in health-care infrastructure and training; (c) additional public health measures; (d) long-term research collaboration with the population; and (e) plans to share financial rewards or intellectual property rights with the study community. The second principle, "Collaborative Partnership," refers to the ability of the study population to make informed, free and uncoerced decisions about their participation in research. The third principle, "Transparency," has two benchmarks: an independent body should create a repository of formal and informal agreements about benefits that are publicly accessible and community consultation should be implemented to inform local populations about these agreements. The authors of this framework argue that these conditions will help minimize exploitation by ensuring fair and scientifically valid selection of the study population, serious consideration of the risks and benefits for participants and their communities, and informed and voluntary participation.

Debates over standard-of-care and specific obligations of researchers to participants and communities at the end of a study are likely to continue. There is general consensus about the desirability of using the best proven and universally acceptable standard of care in clinical trials. There is consensus regarding the importance of providing treatments shown to be effective to communities at the completion of a study. And there is general agreement about the desirability of deciding before a study is implemented how and what benefits will be provided to research participants. Nevertheless, important questions remain unresolved concerning how, exactly, these noteworthy objectives can be achieved in practice. Who is responsible for determining the standard of care? The researchers who design the study, the participating community, the host country IRB, or international sponsors of research? Who should provide the financial resources to ensure sustainability of post-trial therapies? Sponsors of research, governmental funding agencies, or pharmaceutical companies? These questions require concerted efforts on the part of all stakeholders to work collaboratively on developing feasible and sustainable solutions in the context of great economic disparities worldwide. Programmes such as the HIV-NAT drug

fund, established in 2001 by the HIV Netherlands Australia Thailand Research Collaboration to provide continual access to drug therapy for research participants on the basis of a co-payment and sliding scale system, illustrate the need for creative solutions and the potential for successfully implementing them (Ananworanich et al., 2004).

## 3. ETHICAL CONSIDERATIONS FOR INFORMED CONSENT

Informed consent is universally recognized as a key component of ethical conduct in scientific research. Requirements for informed consent in national and international guidelines are based upon and justified by the principle of respect for persons (Faden & Beauchamp, 1986; Levine, 1986; Veatch, 1987; Brody, 1998). Informed consent describes an interactive process in which individuals or their surrogates voluntarily agree to participate in a research study after the purpose, risks, benefits and alternatives have been thoroughly described and understood. Three conditions are foundational to informed consent—the provision of information, comprehension of information, and voluntary participation.

Requirements for informed consent assume that individuals are autonomous agents with the capacity for expressing a self-determined choice. Too often ignored are other assumptions embedded in the notion of voluntary informed consent, assumptions not only about the use of language and the meaning of concepts, but also assumptions about social relationships within families, institutions and communities.

Although national and international policies for informed consent have been established, biomedical and behavioural researchers working in resource-poor settings face considerable challenges (e.g. Bhutta, 2004; Woodsong & Karim, 2005). The primacy of individual autonomy and difficulties involved in applying international standards can be daunting for investigators in the field, particularly when they are confronted with the reality of cultural beliefs about consent that may be in direct conflict with regulatory requirements. As Sugarman and colleagues (1999:2) pointedly observe:

...despite broad agreement about the need to obtain informed consent, there is some uncertainty about how or whether meaningful consent is achieved in practice, whether theoretical understandings of informed consent are useful or practical, and what practices help enhance the possibility that patients and subjects in fact meaningfully consent to treatment or participation in research.

The interrelated dynamics surrounding social power and personal trust are key components in obtaining consent to research. Efforts to obtain informed consent may be compromised when there is an essential lack of trust, particularly if it is based on past experiences of exploitation and the abuse of power by health professionals or other authorities. Additionally, it is naive to assume that informed consent will necessarily protect individuals from harm. Even when it represents an idealized expression of individual choice, informed consent is irrelevant if a study lacks scientific integrity or presents excessive risks for participants and these issues are normally considered by research ethics committees when protocols are reviewed.

This chapter addresses the process of informed consent in social contexts emphasizing factors that influence comprehension of information, the communication of risks, and the locus of decisional authority. The implications of power inequities for the consent process are also explored. Finally, issues associated with the preparation of consent forms and documentation is reviewed.

### 3.1 The process of informed consent: cultural and social context

#### 3.1.1 *Comprehension of information*

Comprehension is a key aspect of the informed consent process and is strongly emphasized in guidelines or recommendations for ethical conduct in scientific research (e.g. National Bioethics Advisory Commission, 2001; CIOMS, 2002; Nuffield Council on Bioethics, 2002, 2005). Even when individuals share the same language, it is often difficult for people to understand information included on consent forms used in biomedical or behavioural research (Ogloff & Otto, 1991; Goldstein et al., 1996; Elbourne

et al., 1997; Davis et al., 1998; Raich et al., 2001). In some cases, participants' lack of comprehension of the nature of the research and the informed consent process may be extensive. In Case 1 (this volume), Henderson & Yu describe serious charges of exploitation made by participants involved in a collaborative project on thymus nuclear protein (TNP) for HIV/AIDS conducted in Henan Province in China (Cyranski, 2005). In this case, participants claimed they did not know why they were chosen to participate, they were not told about the treatment, and they did not understand the informed consent document containing medical terms that they could not understand and which they were asked to sign.

Investigators obtaining consent often must explain sophisticated scientific or medical concepts, particularly in complex trials involving the use of placebos or randomization. This can be challenging for researchers working with communities and individuals in resource-poor countries and populations with a lower level of literacy (e.g. Love & Fost, 1997; Preziosi et al., 1997; Kass & Hyder 2001; Bhutta, 2004; Sankar, 2004; Wang et al., 2004; Adams et al., 2005; Dawson & Kass, 2005; Kass, Maman & Atkinson, 2005; Woodson & Karim, 2005). Wang and associates (Wang et al., 2004) note that randomization and blinding were the most difficult concepts for participants to understand in a clinical trial of vitamins and folic acid to reduce neural tube defects, conducted in China. In their study of informed consent for an influenza vaccine for children in The Gambia, Leach and colleagues (1999) report that, although 90% of the 189 consenting parents knew that the purpose of the vaccine was to prevent disease, only 10% understood the placebo control design. Pace and colleagues (2005) also found that, although most respondents in their study of comprehension of consent to a randomized drug trial among HIV-positive individuals in Thailand said that they were well informed, only one third correctly reported that half of the participants would receive the experimental therapy.

Comprehension of study goals and procedures is often influenced by difficulties associated with the "*therapeutic misconception*" (Appelbaum et al., 1982), the belief that participation in a research study will result in some medical benefit to the participant, even in the case of a placebo control trial. This presents difficulties for investigators working in settings where access to medical care may be compromised by poverty. For example, Molyneux and colleagues (2004) suggest that many parents whose children were involved in studies in a coast town in Kenya believed that their children would derive medical benefit. They argue that this misunderstanding impacts directly on reasons for consent or refusal to a study and contributes to parental concerns about study participation.

Comprehension of the nature of the study does not necessarily indicate that someone understands other dimensions of informed consent (e.g. Elbourne et al., 1997; Sanchez et al., 2001; Joubert et al., 2003). Karim and colleagues (1998), for example, examined consent to a study of perinatal HIV transmission being conducted in a largely black population in South Africa. They found that participants' knowledge of HIV transmission was high, suggesting that most women understood the nature of the research. However, Karim and associates found that 88% of 56 women interviewed said they felt compelled to participate in the study and that most of the women believed that the hospital would not allow them to quit the study. Similarly, in a study of informed consent to research on iron supplementation for pregnant women in rural Bangladesh, Lynoe and associates (2001) report that many of the 105 women in their study did not understand that they were free to refuse participation in the research or that they could withdraw their participation. Additionally, about half of the women believed that the iron supplementation was provided as routine care.

The collection of DNA samples from individuals in developing countries and the establishment of tissue banks for future research have added another dimension to the complexity of consent forms and consent discussions for research (Clayton et al., 1995; Beskow et al., 2001). Obtaining permission for the use of identifiable tissue samples in future research raises serious questions about the complexity of decision-making for consent (Marshall, 2004). For example, how much information does someone need to know about the potential use of stored tissue samples in the future to make an informed decision? What role should families or communities have in making decisions about the future use of samples? The general consensus among genetic epidemiologists and other investigators is that the best strategy for respecting individual choice is to provide someone with a menu of options about future use of the

samples. Although conceptually sound, the “menu” format has several disadvantages. It is not only time consuming for both researchers and potential participants, it also may be confusing for some people.

An individual’s comprehension is always enhanced when researchers engage the study community in active discussions of project goals and procedures through meetings with local leaders or public forums, and when information is provided to potential participants before obtaining consent (Preziosi et al., 1997; Fitzgerald et al., 2002; Wang et al., 2004; Dickert & Sugarman, 2005; Woodsong & Karim, 2005; Rosenthal, 2006). In their study of comprehension during informed consent to research on HIV-1 transmission in Haiti, Fitzgerald and associates (Fitzgerald et al., 2002) report that participants’ understanding of the content of the consent forms increased substantially after meetings with a counsellor during which information about the study was provided; 80% of the 30 individuals participating in this study passed an oral exam before enrolment in the research project. In a study on informed consent to a vaccine trial for measles conducted in Senegal, Preziosi and colleagues (1997) report that parents understood the project sufficiently to make informed choices and that illiteracy was not a barrier to comprehension. The authors suggest that extensive community engagement before obtaining consent contributed to parents’ understanding of the study.

Comprehension is also enhanced through consultation with cultural “experts” and local representatives regarding the most effective ways of communicating with potential research participants about the purpose of the study and the importance of obtaining consent (e.g. Marshall & Rotimi, 2001; Strauss et al., 2001; MacQueen et al., 2004; Dickert & Sugarman, 2005). Investigators might consider conducting focus groups with individuals representative of those who may be recruited to a study in order to understand issues and concerns associated with preparing the consent form and developing approaches to obtaining consent.

Additionally, comprehension may be increased when researchers develop strategies to promote understanding of the research, such as pictorial displays or graphics. Oral or written “tests” might also be used to ensure comprehension. If the concept of a test is culturally unacceptable or not feasible, investigators could ask for feedback from the individual concerning their understanding of the study goals, procedures, risks and other consent elements. As Woodsong & Karim (2005) note, the most important concern for the investigator is developing an approach that facilitates the presentation of information and documentation of a person’s comprehension.

In all cases, consent forms and the process of obtaining consent should be pre-tested before recruitment of participants and the implementation of a study. Pre-testing the consent form assists researchers in validating the content and the process of informed consent to biomedical and behavioural research.

### *3.1.2 Communication of risks*

An informed choice concerning research participation depends upon a clear understanding of the potential risks and harms associated with the study. While this might suggest a straightforward assessment on the part of the person being consented, in fact, there are regulatory, cultural, and psychological factors that contribute to complexities surrounding communication about risks. First, accepted international guidelines for informed consent require that all potential risks must be disclosed to individuals as part of the consent discussion, including, if relevant, the possibility of death. However, disclosing abundant information about potential harms in a direct way may be alarming and frightening for many individuals (e.g. Marshall, 2001; National Bioethics Advisory Commission, 2001; Sugarman et al., 2001; Nuffield Council on Bioethics, 2002; Adams, 2005). Marshall (2001:35), for example, describes the frustration of a Nigerian investigator regarding the lengthy and complex disclosure requirements for informed consent, “Some concepts are completely alien to people. For example, if you tell someone...they are going to die in the process (of doing the study), no one can accept that!” Upvall & Hashwani (2001:191), in their discussion of informed consent for study participants in Pakistan and Swaziland, note that the mention of possible risks “frightened participants”.

Second, the language used to address risks in informed consent documents may be perplexing in part because of different perspectives that researchers and the general public have about the notion of risks (Morgan et al., 2002; Sankar, 2004). Although researchers conceive risk in terms of statistical probabilities, the general public does not. Additionally, it may be difficult to communicate potential risks that are not easily “quantified” or that may be hard for individuals to understand or realistically anticipate. For example, the risks of side-effects from taking medications used in a protocol may raise anxiety among some people, but there is a fairly clear relationship between the procedure (taking the medicine) and the possibility of risk (getting sick from the drug). In contrast, in genetic epidemiological research, it may be difficult to communicate the potential for group harms or stigmatization that might result in the future as findings from genetic research are reported (The International HapMap Consortium, 2004). Communities in developing countries who have not had a negative experience with medical research might be more trustful of investigators collecting DNA samples for future study. A different posture is taken by some American Indian nations, who actively resist participation in genetic research.

Third, there are cultural and social factors that influence beliefs about what actually constitutes a risk or potential harm. In western industrialized countries, for example, drawing a sample of blood is often portrayed in consent documents as posing a minimal risk for individuals. Considered from a medical perspective, drawing a sample of blood normally poses slight risks. Yet blood is characterized as having great symbolic power in most cultural settings throughout the world. This has implications for risk assessment, particularly in settings where blood and other bodily fluids or tissues are sometimes used in sorcery practices or in other ways to harm people (e.g. Taylor, 1988, 1991; Stewart & Strathern, 2004). Nigerian investigators conducting community-based studies on diabetes and hypertension described patients’ fears about both the amount of blood drawn and the possibility that blood samples could be used in sorcery practices (Marshall, 2001). Molyneux and colleagues (2004) also describe concerns among Kenyan parents about the amount of blood drawn from their children for research. Additionally, they noted that some parents were confused about the blood samples, believing that blood drawn from their children might be “pooled” and given to other patients.

Parker & Barrett (2003) explore cultural perspectives on the hazards of medical research. They describe concerns among the Iban of Malaysia that have nothing to do with particular procedures that may be involved in a research study, but everything to do with cultural rituals and practices that maintain harmony and balance within the community and with the spirit world. Parker & Barrett (2003:463) argue, “What they were really concerned about was the potential for dangerous consequences that might arise from the interaction with researchers. Subtle cultural rules came into play when negotiating consent, notably the offering and eating of food, without which it would be impossible to contract such an agreement.” Should a family not offer food, or a researcher not accept it, a condition of *puni* could result. *Puni* refers to a state of imbalance between humans, and humans and spirits that could cause illness or even death to family members, and in this case, researchers. This example illustrates the need for investigators to be sensitive to cultural context when communicating information about potential risks and harms.

The risks associated with particular studies vary considerably and depend, in part, upon the specific objectives of the research and the types of interventions and procedures applied. For example, potential harms and higher risks may be associated with medical research involving physical interventions (e.g. biopsies, lumbar or bone-marrow punctures), psychological research (e.g. determination of personality traits or psycho-analysis), and social and behavioural research in which investigators use methods such as home observations or collect data on sensitive topics such as reproductive histories or illegal behaviour. IRBs and ERCs play a significant role in assessing the risks and benefits associated with a study and stringent requirements for informed consent are imposed when a protocol represents more than minimal risk. However, there is a high level of ambiguity regarding definition of risks and policies for ethical conduct in research do not provide specific guidance for investigators or ethics research committees (e.g. National Research Council, 2003, for a review of these issues for social and behavioural science research).



### 3.1.3 *Decisional authority for consent to research*

International guidelines for informed consent highlight the importance of freedom of choice and personal decision-making. However, beliefs about individual autonomy and decisional capacity are embedded within the social and cultural patterns of community obligations and family ties (e.g. DeCraemer, 1983; Marshall, 1992; Good, 1994). In western industrialized countries where personal autonomy is emphasized, individuals are expected to make decisions about research participation for themselves or through designated surrogates. In contrast, in many non-western settings, family members, or community leaders may play a significant role in decisions concerning medical research (Barry, 1988; Hall, 1989; Levine 1991, 1993, 1996; Barry & Molyneux, 1992; Christakis, 1992; IJsselmuiden & Faden 1992; Kuczewski & Marshall, 2002; Molyneux, 2005b; Hyder & Wali, 2006). In culturally diverse resource-poor environments, strict interpretations of requirements for individual consent may be challenging.

In early reports, Ajayi (1980) and Ekunwe & Kessel (1984) suggested that in certain regions of the world, respect for family and community elders strongly influence a community's receptivity to participation in medical research. In her discussion of AIDS research in Africa, Barry (1988) explored difficulties in translating the concept of autonomy in areas where personhood is defined by one's tribe, village, or social group, noting that community leaders or family members of the research participant may need to be approached.

More recently, in their survey of 540 investigators from developing countries, Kass & Hyder (2001) found that 66% thought that the informed consent process focused too much on the individual rather than on the family or community; in research with adults, 19% sought permission from another family member rather than the participant, and this was more likely to occur in situations in which oral, not written, permission was obtained. Sugarman and associates (2001) also found that investigators interviewed about ethical issues in international research reported concerns about the over-emphasis on individual consent required by international guidelines.

Loue, Okello & Kawuma (1996) recognize similar issues in their discussion of the social context of informed consent to research in Uganda. Although Ugandan civil law states that an 18-year-old male living at home has the legal right to make his own decisions, it is customary for the son to obtain his father's consent prior to entering into any obligation or contract, including participation in research. Moreover, some Ugandan women seek the consent of their husband before making a decision regarding their own participation in research. In many traditional societies in resource-poor areas throughout the world, seeking permission from one's husband may be customary. In Case 3 (this volume), Ngare notes that women in rural Kenya being asked to join a study testing a new drug for malaria were reluctant to speak with the researchers unless the researchers had first talked with their husbands. In a study of informed consent practices for genetic epidemiological research on hypertension and breast cancer in Nigeria, Marshall (2004) reports that preliminary results indicate nearly one third of more than 400 married women interviewed said they needed spousal permission to participate in the study of genetics. Marshall (2004:79) describes the complexities surrounding the negotiation of "permission":

In one case, a woman was asked directly what she would do if her husband said he would not allow her to participate in the breast cancer study. She replied that she would wait, than talk with him again, perhaps after cooking him a good meal. She was asked what she would do if he still refused. She replied that she would give him time to think about it, and bring it up again. She also indicated that if he remained reluctant, she would try other ways to influence his decision, including seeking the help of individuals he respected.

As this example reveals, persuasion can be a powerful tool. In this context, seeking permission does not necessarily mean a loss of personal autonomy. Results of the in-depth interviews with the Nigerian women suggest they distinguish between their experience of self determination and their need, in some cases, to convince their husbands of the relevance and importance of the research to them personally. Additionally, as Marshall (2004) points out, it is important to remember the variability that exists not just across cultures, but within particular social settings. In the informed consent study on

genetic research in Nigeria, not all the women interviewed needed to obtain permission from their husbands to participate in the study.

International guidelines and recommendations call attention to the overriding importance of individual consent to research (e.g. National Bioethics Advisory Commission, 2001; CIOMS, 2002; Nuffield Council on Bioethics, 2002, 2005). The CIOMS (2002:73) guidelines, for example, state that:

[O]nly the informed consent of the woman herself is required for her participation. In no case should the permission of a spouse or partner replace the requirement of individual informed consent. If women wish to consult with their husbands or partners or seek voluntarily to obtain their permission before deciding to enrol in research, that is not only ethically permissible but in some contexts highly desirable. A strict requirement of authorization of spouse or partner, however, violates the substantive principle of respect for persons.

The CIOMS guidelines include a stronger defence of women's autonomy than the recommendations by the National Bioethics Advisory Commission (2001), which permit a research ethics committee to recognize the legitimacy of spousal authorization if requested by a researcher with proper documentation (see Macklin, 2004:144). Macklin (2004) is ambivalent about allowing exceptions that would include approaching a woman's husband or father before speaking with her directly. Macklin (2004: 144) argues that, if it is true that research may be prohibited without spousal permission, there is a danger of perpetuating or reinforcing a practice that keeps women subordinate to men and which "...violates the principles of respect for autonomy and equal respect for women." Macklin concedes, however, that spousal consent could be justified if the consequences of not conducting the research would be severe.

When consent is viewed as a process, not a single event, the result is greater flexibility in devising strategies that honour both expressions of individual autonomy and cultural norms regarding the involvement of family members or others who may be important in making decisions about research participation (e.g. Woodsong & Karim, 2005).

### **Community consultation**

In some culturally diverse settings throughout the world, investigators must seek approval from community leaders or tribal elders before implementing a study. Tribal leaders of American Indian populations, for example, have the power—as representatives of sovereign nations—to veto or to allow the participation of members in scientific research. While meeting with councils of appointed or elected elders or other designated authorities to seek formal or informal approval of a study might be necessary in some contexts, it does not replace the fundamental concern with obtaining individual voluntary consent (e.g. IJsselmuiden & Faden, 1992; Macklin, 1999, 2004; CIOMS, 2002; Nuffield Council on Bioethics, 2002, 2005; Emanuel et al., 2004).

Historically, in the area of public health and community development, investigators have developed various strategies to involve local populations in the implementation of project goals (Macaulay et al., 1999; MacQueen et al., 2001; Strauss et al., 2001). Ideally, community consultation and active engagement in research represents a reciprocal and dynamic process that serves to educate both the researchers and the individuals and communities involved in a study. In recent years, scholars have discussed the strengths and weaknesses of approaches to community consultation (Dickert & Sugarman, 2005), particularly its implications for genetic research with culturally diverse groups (e.g. Juengst, 1998; Foster et al., 1999; Weijer, 1999; Weijer et al., 1999; Davis, 2000; Sharp & Foster, 2000; Weijer & Emanuel, 2000; Clayton, 2002). The concept of community consultation highlights the need for researchers to address the question of how a "community" is defined (Juengst, 1998; Davis, 2000; MacQueen et al., 2001). Communities have been characterized as populations of individuals who share collective interests or a common identity (historical or social) that differentiates them from "others." Thus, a community may include people who share attributes such as a common language, ethnic identity, or religion. The concept of community is malleable, crossing the boundaries of historical ancestry, geography, cultural and ethnic identification, social class, behavioural inclinations, and health status.

In their thoughtful review of paradigms for community involvement in research, Sharp & Foster (2000) outline several approaches for group participation, ranging from informal negotiations with community leaders or representatives to full participation of a community advisory committee at every stage of the research. Issues associated with negotiating community participation in biomedical or behavioural research are complex. In her exploration of informed consent to genetic epidemiological studies being conducted in Nigeria, Marshall (2001:chapter 19) found that an important area of concern for investigators was the issue of community approval for research, particularly in the more rural areas; one investigator reported the following:

To enter a community you need to carry that community along with you. There are imperatives...[You must communicate] with the Chief and his council and some others leaders from the community. The individualism that exists in the West does not exist here.

In their survey of more than 500 researchers from developing countries, Kass & Hyder (2001) found that more than half sought approval from a community leader or village elder for documenting consent or informing participants about their study. Researchers who obtained verbal consent for their studies were more likely to consult with community leaders. In a comparable survey conducted with 302 researchers from the USA who worked in international settings, 39% reported seeking approval from a village leader (Kass & Hyder, 2001). In their study of consent practices for research in a poor area of Kenya with high rates of illiteracy, Molyneux and colleagues (2005b) found that discussions with village chiefs and elders were considered necessary to gain permission to implement research in the area, but local leaders could not consent for individuals or family households.

King (1999:211) asked epidemiologists attending an international meeting about informed consent and the practice of seeking approval from community. Researchers who had conducted studies in Africa, Burma, China, the Philippines, South America, and Thailand, agreed that they often required the consent of village leaders to talk with individuals, "because that gave them the credibility they needed to begin the informed consent process with individual community members." The investigators surveyed noted that community leaders in urban areas had less authority than in rural areas because urban populations are more diverse and mobile. Leach and colleagues (1999) also found urban-rural differences in beliefs about the importance of community elders in decisions regarding research participation in their study of informed consent with parents whose children participated in a vaccine study conducted in The Gambia. While parental consent conformed to western standards, among the 189 parents interviewed, 25% of the rural parents, compared to only 10% of the urban parents, agreed that the village chief should have some input concerning the decision to participate in the influenza vaccine trial.

While bioethicists, and policy-makers generally acknowledge that community approval does not and should not replace individual consent, this may be confusing for some individuals. In their description of informed consent for a vaccine trial in rural Senegal, Preziosi and associates (1997) note that, "During the pilot test of obtaining individual informed consent for their children's participation, some women said they were confused by being asked to give their consent, which they believed they had already done during the [group] meeting."

Although there are obvious benefits associated with community consultation and the active participation of community advisory boards in medical or social research conducted in resource-poor settings, Juengst (1998) and Weijer (1999) claim that individuals and communities may have competing interests regarding study participation. One of the most important issues concerns community representation (Marshall & Rotimi, 2001). Additionally, community consultation necessarily involves engaging with local power structures and, in some cases, researchers may inadvertently influence community dynamics. In Case 4, Adebamowo (this volume) examines the impact of researchers on community dynamics and the negotiation of local power and authority in his description of the establishment of a community advisory board in a country in sub-Saharan Africa.

Approaches to consultation and engagement with local leaders and community members will vary depending upon the setting and the nature of the research. However, regardless of the particular strate-

gies implemented, community consultation should not be viewed as a single event, but rather as an ongoing and reciprocal process in which the community—and the individual study participants—are kept aware of research activities and findings and conversely, the researchers are reminded of concerns about the study and its implementation.

#### 3.1.4 *Communication, social position, and power inequities*

Trust is fundamentally important to the process of communication during informed consent (Kass et al., 1996; Molyneux et al., 2005a). An individuals' or community's past experience with research and factors associated with social status and power influence levels of trust experienced by those invited to join a study. Socioeconomic background, caste, gender, age, and education reinforce differences in the relative power experienced by individuals during the consent discussion and this has implications for trust and voluntary participation (Ware & Kleinman, 1992; Barnes et al., 1998; Kuczewski & Marshall, 2002; DeCosta et al., 2004). Uvall & Hashwani (2001:191) speak directly of the complexities associated with negotiating social status, gender and power:

If men in the village are the ones to provide consent for participation of their wives, mothers and sisters, will the participant feel that she can then say 'no'? When she does participate, how freely will she share her thoughts and feelings? How can she be adequately reassured that her responses will not be reported to the male consentor?

In Case 3 (this volume), Ngare describes the emphasis placed on a woman's deference to her husband and "being polite" to outsiders or visitors in rural Kenya. He questions the implications for voluntary consent, particularly for women. Similarly, in Case 6 (this volume) De Costa's description of a study examining low birth weight in rural India calls attention to the normative expectations about treating "outsiders" politely, especially those perceived to be in a position of social authority. De Costa points out that, although the researchers were of the same nationality, many were men, educated, and from the urban centre. In this case, women may not have felt empowered to refuse participation.

In some cases, participation in medical research may be the only means of securing medical therapy, which exacerbates the potential for misunderstandings or undue influence (e.g. MacQueen et al., 2004). In recent years, the AIDS pandemic has shown how access to drug therapy can influence an individual's choice about joining a study. This is particularly true in resource-poor settings in developing countries. In Africa, for example, where more than two thirds of the world's HIV-infected individuals reside, health-care infrastructures are weak and insufficiently funded (e.g. Whalen et al., 1997; Fauci, 1999; Harries et al., 2001; Rabkin et al., 2002; Reynolds et al., 2003). Developing countries such as Kenya and Uganda have established comprehensive programmes for HIV/AIDS care and support, but there remains a large gap between the number of people who actually need drugs and other medical support and the number who have access to them (e.g. Mutuluza, 2002).

It is not only in the area of HIV/AIDS that the possibility of access to health care or access to treatment plays an important role in motivating individuals to participate in biomedical or behavioural research. The voluntary nature of consent for participation may be questionable when individuals feel compelled to participate in a project in part because they believe that if they do not, their medical care will be affected (e.g. Molyneux et al., 2004; Lynoe et al., 2001). Karim and colleagues (1998), for example, found that 28% of the 56 women enrolled in a study of perinatal HIV transmission conducted in South Africa said that they agreed to the HIV test because they thought that refusing would compromise their medical care; they argue that although consent may have been "truly informed" among this largely black population, it was not "truly voluntary."

Reports of abuses associated with informed consent to research in resource-poor settings consent call attention to global power inequities when research is conducted by investigators sponsored by organizations or pharmaceutical companies from industrialized nations. In a clinical trial of the antibiotic trovafloxacin (Trovan) in the treatment of bacterial meningitis in Kano, Nigeria (Khabir, 2001), researchers working for Pfizer Pharmaceuticals were charged with neglecting to obtain adequate con-

sent. Similarly, problems surrounding informed consent were reported in a clinical trial for a drug called VGV-1 in China (Cyranoski, 2005). Participants from Henan province claimed that informed consent practices were neglected and they were not told about the risks of side-effects from the drug.

The potential for undue influence on individuals considering participation in a study will always be a factor for impoverished communities with inadequate and insufficiently funded health services. Ultimately, the only solution lies in global efforts to reduce health disparities and access to care so that individuals are able to make an informed and voluntary decision about participating in a study.

## **3.2 Preparation and documentation of the consent form**

### *3.2.1 Language*

Both the form and the content of procedures for informed consent are influenced by the possibilities and limits of language. Misunderstandings and miscommunication about the elements of informed consent are more likely to occur when investigators and participants speak different languages and when informed consent documents must be translated. Although international guidelines for informed consent stress the need for clarity and simplicity, the actual language of consent forms may be confusing or obfuscating. Taken together, the length of consent forms and their legalistic format can be intimidating for someone being asked to participate in biomedical or behaviour research. In their research with investigators conducting international studies, scholars (Kass & Hyder 2001; Sugarman et al., 2001; Dawson & Kass, 2005) found that many investigators do not believe that the legal language required on consent forms is meaningful to study participants.

The complexity of scientific concepts associated with research and the need to explain them in the consent discussion, especially when there are no equivalent expressions for particular biomedical terms, exacerbates difficulties surrounding the translation of informed consent documents for resource-poor communities in international settings. In a survey of researchers from the USA working internationally, and in focus groups conducted with researchers in the USA and resource-poor nations, Kass & Hyder (2001) found that many investigators expressed concern about the translation of scientific concepts. One investigator from the USA pointed out, "In many African languages, there is no word for 'research' or 'science.' The word used is generally the same as the word for 'medicine'" (Kass & Hyder, 2001:B26). In their study of parental consent for studies involving blood samples from children in Kenya, Molyneux and colleagues (2004) also report that many members of the community are unfamiliar with the concept of research and there are no "commonly used, universally understood words" for research. Similarly, Marshall (2004) reports that Nigerian researchers involved in genetic epidemiology noted that some concepts could not be easily translated because there are no linguistic equivalents for terms such as "genes" or "candidate gene". However, a broader understanding of inheritance in relation to physical traits or diseases such as sickle-cell anaemia facilitates discussion of genetic research in communities where linguistically equivalent terms do not exist.

The process of back-translation is routinely applied when consent forms must be translated from one language to another. This process begins with the translation of the consent form (or other research document) into another language. The form is then given to a native speaker who translates the document back to the original language. This process ensures the validity of the translated form and provides opportunities for corrections to be made. Particular attention must be given to the appropriate use of local dialects and terminology that effectively communicates the meanings of words to potential research participants.

In addition to the lack of equivalent or similar words that may be used in translation, the process of translation itself may result in misrepresentation of the research. For example, Achrekar and Gupta (1998) compared the Thai translation of a consent form for a placebo-controlled trial of zidovudine to reduce maternal-fetal transmission of HIV with the original English version. They found very different descriptions of the use of a placebo in the two forms. Sugarman and colleagues (2001:E6) also report

that investigators interviewed about ethical issues in international research described awkward situations involving translation:

[I]n a study that required a careful assessment of the frequency of vaginal intercourse, the term coitus was translated to 'with your husband,' yet this may have led to an incomplete measure of the frequency of vaginal intercourse with all partners.

The use of an interpreter may reduce language barriers to consent. However, interpretation is a complex process in which not only languages, but also cultural and contextual factors, are translated (Kaufert & O'Neil, 1990; Marshall, 1992; Kaufert & Putsch, 1997; Barnes et al., 1998; Kaufert et al., 1998; Marshall et al., 1998). A broad range of other issues surround the interpretation process such as paraphrasing that may result in omissions or erroneous substitutions of words, different levels of comprehension among individuals involved in the discussion, and conflicting cultural beliefs. Moreover, drawing on their research with native Canadian medical interpreters, Kaufert & O'Neil (1990) found that native interpreters often introduce their own beliefs and personal agendas into the interaction.

In their analysis of communication through interpreters in health-care settings, Kaufert & Putsch (1997) explore ethical dilemmas that arise from differences in class, culture, language and power. They argue that in multicultural contexts, understanding the use of language is crucial in developing a more culturally sensitive approach to health-care decisions. Carrese & Rhodes' (1995) examination of the use of language and its implications for disclosure of medical information among the Navaho nation in the USA illustrates the powerful constraints that language can have on medical interactions. Carrese & Rhodes (1995) note that avoidance of "negative talk" is an important cultural value for many Navahos because discussing negative events may actually cause them to happen. In this case, cultural values that would prohibit discussion of adverse events or potential harms associated with medical research are in direct conflict with international guidelines for consent that require complete disclosure of risks, including the possibility of death.

The language of consent documents requires thoughtful attention not just to the words that signify research concepts, but also to cultural factors that influence interpretation and the social dynamics of communication. The involvement of native speakers is crucial to the successful translation of documents and their application in the field. Pre-testing consent forms with individuals from the study population provides useful direction concerning the need to revise consent forms so that they are meaningful and understandable for study participants.

Although investigators are encouraged to use simplified forms with clear language (e.g. Freeman, 1994), a study by Davis and associates (1998) found that, when they compared standard and simplified consent forms, comprehension was low with both types. Lowering readability level alone does not necessarily result in increased comprehension. However, in resource-poor countries, higher rates of illiteracy may contribute to challenges associated with comprehension of informed consent documents (Ekunwe & Kessel, 1984; Christakis, 1988, 1992; Levine 1991, 1993, 1996; El-Sadre & Capps, 1992; Marshall et al., 1998; Kass & Hyder, 2001). Sriram and associates (1991), for example, studied informed consent in clinical practice in Bangalore, India, and found that physicians reported that it was difficult to obtain consent from illiterate patients. These investigators also report that nearly one third of the 148 patients and 60 doctors interviewed believed that provision of information could sometimes be harmful. Similarly, Macpherson & Connolly (2002) describe the phenomenon of "information overload" which created anxiety among participants in a study of the prevalence of human T-cell lymphotropic virus type-1 (HTLV-1) and the rate of vertical transmission from mother to child in Grenada.

### 3.2.2 Documentation

Requirements for written signatures on consent forms emphasizes the legalistic rendering of the consent as a signed contract rather than a social process. Viewed from this perspective, critics claim that informed consent functions more to protect the interests of institutions and researchers rather than those of the participants.

Obtaining written signatures may be difficult when communities have suffered politically, socially, or economically because of signing “legal” forms that resulted in sanctions against them, or in cultural settings where agreements based upon trust do not require a signature. In their comparison of informed consent in Pakistan and Swaziland, Upvall & Haswani (2001:191) note that some participants might find it threatening to sign a document when they are illiterate or do not understand its contents, particularly if signing (or using a thumbprint) might only be used for marriage documents or for other significant life events. Kass & Hyder (2001) found that investigators working in developing countries were concerned about the necessity of signatures; a focus-group participant observed that, “In [Latin America], particularly those with limited reading ability are very hesitant about signing things...Our insistence on informed consent is seen as culturally insensitive but was accepted out of understanding of our needs to satisfy our funding agency and government regulations” (Kass & Hyder 2001:B24).

Similarly, Sugarman and colleagues (2001:E7) report that investigators working in developing countries suggest that occasionally the requirement for written consent may be inappropriate: “[I]n one project involving many illiterate subjects, although thumbprints might be considered to be an appropriate means of documenting individual consent, local investigators did not use such an approach because it was too closely related to past police tactics and was believed to frighten potential research participants.” In interviews with Nigerian researchers, Marshall (2001) reports similar findings. One investigator noted that, “Even if they use a thumbprint, they can get suspicious. They can’t read so they wonder why you need their thumbprint. It’s a big fear...the issue has to do with government documents. It’s threatening because they don’t know what they are signing or what they might be giving away” (Marshall, 2001:C21).

International guidelines recognize the validity of verbal consent when written consent is either inappropriate or unacceptable but only when it is properly documented (Council of Europe, 1997; Nuffield Council on Bioethics, 2002, 2005; World Medical Association, 2000; CIOMS, 2002). The Nuffield Council on Bioethics (2002:82), for example, recommends that if requesting a person’s signature is inappropriate, then other means should be devised for documenting consent, such as an audio-taped recording, or an independent witness for verbal consent. In their recommendations for ethical conduct in clinical trials conducted in developing countries, the National Bioethics Advisory Commission (2001:Vol. 1:50) suggests that USA research guidelines should be amended to allow ERCs to waive requirements for written and signed consent forms to accommodate local cultural norms.





## 4. CASE ANALYSES: ETHICAL DILEMMAS IN HEALTH RESEARCH IN RESOURCE-POOR SETTINGS

The following ten cases illustrate the challenging ethical issues faced by investigators in the implementation of biomedical or behavioural research conducted in resource-poor settings throughout the world. The cases were contributed by health professionals working in China, Haiti, India, Kenya, Malawi, Pakistan, Papua New Guinea, Russia, sub-Saharan Africa and Uganda. The cases include descriptions of the study, the primary ethical dilemmas confronted by researchers, and recommendations for good practice.

### CASE ONE

#### **Old problems but new challenges: ethics review and informed consent in a clinical trial for HIV/AIDS in China**

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#### **Case description:**

On 12 January 2004, Mr Wan Yanhai, an AIDS activist in China, publicized an “open letter” addressed to the institutional review board (IRB) of the National Center for AIDS/STD Control and Prevention (NCAIDS) of China on behalf of 19 study participants. The “letter” raises a series of questions about possible ethical and legal problems related to a collaborative clinic trial project on thymus nuclear protein (TNP) for HIV/AIDS by New York International Commerce Group Inc. and Viral Genetics of USA, NCAIDS and Beijing XX Hospital of China.

According to the letter, the 19 AIDS patients (12 males and 7 females) from YY Village of Henan Province reported “serious violations” of ethical principles during a clinical trial conducted by the hospital. In February 2003, doctors and nurses from XX Hospital went to YY village and collected blood samples from 100 people with HIV/AIDS. Eighteen of them were later notified and came to the hospital for “treatment.” According to the letter, they did not know why they were chosen, nor were they told the nature of the treatment. Later they were asked to sign the consent forms, though they could hardly understand their contents, which included many medical terms, including some in English. In fact, some of these 19 patients were illiterate and none knew any English, but they still all signed the consent forms, saying that they trusted the government medical staff and wanted to get treatment. They did not receive copies of the forms.

The patients said that they were later discharged from the hospital but came back for follow-up blood tests each month. During the follow-up period, 2 out of the 19 patients died. But the hospital refused to address their concerns about the deaths. The patients did not receive any test results, or explanations of test and examination results.

The patients did receive some compensation during the study and follow-up period for transportation and a daily allowance for the 3 months they stayed in the hospital. But there was no other compen-

sation for the follow-up period, which lasted as long as 8 months, and the patients claimed that compensation for the blood tests was inadequate.

The patients thus requested the IRB of NCAIDS to help them and protect their interests. Some of them had searched the internet and had heard that the "Helsinki Declaration" was meant to protect human subjects. They asked for copies of the study proposal, the informed consent form and the medical records. They also sought explanations for why some patients died or became more ill during the follow-up period. They requested additional compensation and allowance to cover the trial, the follow-up period, and for work lost.

The hospital, on the other hand, stated that the study was carried out based on their desire to save the lives of patients with late-stage AIDS. All 19 selected patients had CD4 counts of less than 50<sup>3</sup>, which is considered very low in any region of the world, and without effective treatment, they would die within two years. At the time the trial was carried out, there were no antiretroviral drugs available on the market. The study protocol was submitted and reviewed by the IRB of XX Hospital, and was subsequently approved. All the study participants were given several days to understand the study before informed consent was obtained. They did, however, agree that there were shortcomings during the consent process. They recognized that the patients, who were mostly illiterate, poor farmers and desperately seeking life-saving drugs, would not pay much attention to the terms and explanations of the study, but hurried through the consent process in order to get the medicines. They did not insist on giving each participant a copy of the consent form, saying it was useless for illiterates, and acknowledged that it was wrong to charge for photocopying consent forms when the patients requested them. In fact, the consent forms were kept together with the case history files, photocopying of which, according to the hospital regulations, entailed a charge. As for the other forms of compensation, according to the hospital, the patients had been reimbursed even though this was not stated in the consent form.

The hospital stated that there was no evidence that the deaths of the two patients during the follow-up period were related to the drugs used. They explained that the participants were all late-stage AIDS patients whose deaths were linked to the progression of the disease, not the consequences of the trial.

On the basis of the request of the relevant parties, the IRB of NCAIDS organized a special IRB meeting on February 18, 2004, with invited participants including principal investigators and representatives from XX Hospital, representatives of study participants and AIDS activist, Mr Wan Yanhai. After reading through the documents, listening to the presentations of all parties, and discussion among the IRB members, the IRB of NCAIDS concluded that there was no serious violation of ethical principles and infringement on the rights of the participants, based on the available evidence and information. This was because: (1) the project had been approved by the IRB of XX Hospital; and (2) the doctors read the informed consent document and obtained the signatures of all participants, which was testified by the witness's signatures.

However, the IRB of NCAIDS gave a number of suggestions to improve the ethical standards of clinical research at the hospital:

- Each of the study participants should be given a copy of the consent form, and the issues and concerns about the study should be carefully explained to the participants;
- A subsidy of RMB 10 Yuan per day should be provided to the participants during the follow-up period in Beijing;
- In future work, especially during the recruitment and informed consent process, more detailed instructions should be given to the study participants, especially to vulnerable populations;
- The wording of the informed consent document should be straightforward and easy to understand, given the literacy level of the study participants. Chinese explanations must be given for English terms.

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<sup>3</sup> 0.05 x 10<sup>9</sup> per litre

**Primary ethical challenges:**

There are universal challenges involved in achieving truly informed consent for trials at big city hospitals that enrol farmers with a low level of education and who are stigmatized by AIDS. When no alternative to antiretroviral treatment is available outside the trial setting, subjects' voluntary participation is often questionable. Improving voluntary, informed consent in a country lacking a historical and cultural focus on individual rights may be facilitated by access to the internet and the help of AIDS activists, and, in this case, by taking the extraordinary step of making a public complaint to higher authorities. However, this case also highlights confusion about the roles and responsibilities of IRBs charged to review collaborative studies, especially in international collaborations. In this case, the IRBs of the pharmaceutical companies and the hospital should be the ones to review the study protocol, but the system did not function adequately to protect the research participants. When a project involves multiple institutions participating, it is critical to understand how many and/or which IRBs should be responsible for initial review and oversight. IRBs should be independent, but it is not clear what the role of an IRB should be when asked to be a referee from the outside.

**Good practice recommendations**

- Training in research ethics should be strengthened for investigators, particularly when studies involve participants from communities with low literacy.
- Researchers must recognize that informed consent is a dynamic process of communication to ensure voluntary and informed participation, and not simply the request for a signature or thumbprint.
- Ethical review of research protocols in resource-poor settings should be improved.
- Responsibilities of multiple IRBs involved in a single project must be clarified to avoid confusion.
- Regulation of ethical review of clinical trials by private companies from resource-rich countries is needed.
- Educate institutional review boards and ethical review committees concerning appropriate methods to protect confidentiality for the study population.

## CASE TWO

### Designing a group-based intervention to promote condom use in HIV serodiscordant couples in three countries: India, Thailand and Uganda

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#### Case description:

The study “Phase 1 trial of an intervention to increase condom use by HIV-serodiscordant couples” was designed by USA and local investigators and study staff to assess the feasibility of using the same group-based intervention for couples to promote condom use by HIV-serodiscordant heterosexual couples in three diverse sites (India, Thailand, and Uganda). The study protocol enrolled participants who had been identified as being infected with HIV in other research studies at each site. These men and women were designated as index cases and were asked to bring their primary sexual partner for HIV counselling and testing. If the members of the couple were determined to be serodiscordant, they were individually consented and then they were enrolled to participate in the group intervention. The intervention required participants to attend four group sessions: two same-sex groups of mixed serostatus and two groups of couples. Participants were interviewed at baseline, after the intervention, and at one month and three months after completion of the group sessions.

#### Primary ethical challenges:

The design of this study posed a number of ethical challenges associated with informed consent, disclosure of seropositivity to a partner, and beliefs about appropriate gender roles. Investigators faced additional challenges because they worked at three different sites that varied culturally and epidemiologically. Each of the three sites in India, Thailand, and Uganda had developed systems for evaluating scientific protocols, including IRBs to review written consent forms and study designs. The protocol was reviewed by IRBs in the USA and at participating institutions in each country.

Conflicts did not arise at any site. This is likely to be due to the fact that the study was incorporated into an existing research structure and employed staff and facilities that had been conducting the HIV research during which the index cases were initially identified. These staff had extensive experience in conducting research with individuals who were HIV-positive.

*Informed consent:* The study protocol involved multiple levels of consent. To participate, HIV-infected participants had to be willing to disclose their HIV status to their sexual partner, to ask that partner to present for testing and counselling, and to agree to participate with their partner in the intervention groups. The partner had to be willing to receive counselling and testing for HIV, to disclose his/her status to his/her partner, and participate in individual and couple intervention groups. The couple was not eligible for enrolment if the partner was HIV-positive. Individuals provided consent once, rather than being asked a second time for consent for participation in the group, after determining their serostatus. However, individuals were informed that they could withdraw from the study at any stage. This approach to informed consent worked effectively at all sites despite the cultural differences. Researchers spent time discussing the study and providing information to potential participants before obtaining consent.

*Disclosure, right to privacy, and the “right to know” of the HIV-negative partner:* As noted, participants had to disclose their HIV status to their partner if they had not already done so. Other privacy issues involved the requirements that participants be interviewed about attitudes and sexual practices and that they participate in group activities. Group activities did not require participants to specifically disclose their status to others, except to the extent that the groups were for HIV-serodiscordant couples. Group sessions did, however, require couples to discuss barriers to condom use and issues related to sexual communication and negotiation. These activities were undertaken using a variety of approaches, including role plays, listing exercises, and games in order to increase comfort level and permit individuals the opportunity to participate without revealing personal information. Additionally, participants were also asked to do “homework” in which they practiced some of their skills and reported back to the group about what they did. Although no adverse effects were reported at any site, follow-up interviews to specifically address the experience of participants in group activities were not conducted.

*Respect for local values regarding appropriate gender roles:* A central point of discussion among the investigators during development of the protocol was the appropriateness of including intervention sessions that required couples to attend group sessions with their partner. The research team was concerned about the possibility that the group sessions might constitute a violation of local norms that prohibit discussion of sexual issues among men and women. The investigators believed that this concern was balanced by the need to provide an intervention to serodiscordant couples, an underserved cohort at identifiable risk of HIV transmission. All groups openly discussed “taboo” subjects and no problems were reported at any site.

The project team also had to address the potential for harm to participants as a result of disclosure and efforts to reduce risk. The research team was particularly concerned about the ability of HIV-infected women to disclose to a partner, thus risking self-identification as having previous or current sexual partners outside the couple, and potentially risking physical harm as well as possible emotional, economic, or social harm. This concern was balanced against the risk to the individual who was HIV-negative of having unprotected sex with a partner they did not know was HIV-positive.

Similarly, there was concern regarding the ability of women who were not infected with HIV to successfully bring up the need for condoms and negotiate their use. This issue touches on a variety of local beliefs about sex and gender roles, including the appropriateness of women discussing sex with their partner. Additionally, requesting condom use, even in the case of a partner known to be infected with HIV, may violate norms regarding women’s duty to be subordinate to men.

The possibility of domestic violence against women who either disclose their infection or request condom use posed special challenges. The study investigators, study staff, and funders discussed various ways to handle this risk. It was ultimately decided that participants would be ruled ineligible if they reported any history of domestic violence with this current partner. Additionally, participants were urged to report any instance of domestic violence that occurred during the study.

The successful implementation of this study demonstrates that even in widely diverse cultural contexts such as India, Thailand, and Uganda, cultural taboos concerning disclosure, gender roles, discussion of sex, and violence against women can be mitigated through intensive staff training and focused attention on the needs of men and women confronting AIDS. Such efforts are enhanced, however, when international and local investigators are equal collaborators in the design and implementation of studies. International, multisite, collaborative research projects require flexibility and creativity in balancing the need for core consistency across research sites with the need to consider the unique cultural environments in which studies are implemented.

### **Good practice recommendations**

- Conducting research into HIV prevention in culturally diverse settings requires local knowledge about gender roles and the negotiation of sexual activities, including discussions about sexual issues.
- Successful implementation of study interventions depends upon highly trained research staff who are sensitive to local cultural context and the special needs of persons with HIV.
- Collaborative partnerships must be strengthened between researchers in resource-rich and resource-poor settings.

## **CASE THREE**

### **Clinical trial of antimalarial drugs in Kenya**

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#### **Case description:**

Dr Alex is a faculty member in the medical school of a university located in a rural area in Kenya. He has developed a strong interest in malaria research. After developing a proposal for a clinical trial of a new therapy for malaria, he submitted his protocol to the university IRB. The IRB required written informed consent rather than verbal consent.

The study site was a rural area inhabited by one of the 42 ethnic groups in Kenya. The area is characterized by poverty and a high level of illiteracy. The study population included men and women aged 25–60 years. The culture of this ethnic group recognizes the man as the head of the household and believes that he should grant permission before anything happens in the family. The culture also dictates that it is good practice to welcome visitors into the community and discourages disappointing them. Therefore, visitors are received warmly and almost anything they request will be provided without resistance. Access to health care for this population is difficult not only because of the distances to a health-care facility, but also because of economic inaccessibility associated with poverty. Additionally, health-care facilities are poorly stocked with drugs and therefore, patients usually are requested to purchase drugs from the local pharmacies.

Dr Alex arranged to recruit and train 10 research assistants who were medical students in their final year of studies. The training covered the subject matter of the research as well as the process of obtaining informed consent.

In this community-based double-blind placebo-controlled study, the sampling procedure was clearly documented and the sample size was predetermined. Research assistants were informed that both the female and male heads of each selected household had to be interviewed separately and consent obtained from each independently.

The medical students enjoyed going to the field wearing their white coats. Whenever they arrived at a household they would introduce themselves and seek informed consent. All elements of informed consent were discussed and respondents were told that they were required to sign the consent form.

The research assistants were surprised that, even before completing their explanations of the project, individuals would consent to join the study. Moreover, before they began administering the questionnaire, most respondents wanted to discuss health problems they had been experiencing in the hope that they would get treatment. The research assistants also noted that the women seemed reluctant to discuss anything if they were approached before their husbands and that, before agreeing to be interviewed, the husband needed to give his approval. If he refused, the woman could not be interviewed. Moreover, although some women were reluctant to be interviewed, they did not say that they were unwilling because their culture does not allow them to show disrespect to visitors.

Additionally, the researcher assistants encountered reluctance to sign the consent form among individuals who were illiterate. Some respondents could not understand why they were being asked to sign the forms when they had already consented to being interviewed and taking part in the clinical trial.

### **Primary ethical challenges:**

It is notable that the research assistants were amazed at the almost instant acceptance to participate in the study by the majority of the respondents. There are several reasons that explain this phenomenon in this particular study population, which is similar to most rural communities in Kenya. First, wearing a white coat symbolizes being a doctor. Many people in the rural population do not distinguish between different types of health personnel. The doctor is associated with giving care. In this study, respondents may have seen an opportunity to be attended to by a doctor, hence the quick granting of consent. Although research assistants explained that this was a study, the drugs provided for the clinical trial may have been viewed as treatment. Since the respondents generally had problems obtaining drugs, they may have thought this would be an opportunity to get free drugs. Second, a doctor is a highly respected person in society and therefore, whatever the doctor is doing must be "right." This belief makes it difficult for them to decline what the doctor is requesting. The doctor is often perceived as a powerful person capable of performing "miracles." Third, it is an important social value in this community is treating visitors in a friendly manner. Declining a request made by a visitor is viewed as being disrespectful and not conforming to traditional values. Fourth, the notion of individual consent is in conflict with traditional values about who is able to make decisions in the family. While western bioethics recognizes the rights of the individual, in some settings particular cultural beliefs complicate the interpretation of these rights. In this community, the male household-head normally gives permission to his wife for her to consent to take part in the study. If he declines, although she may be willing to participate, she cannot because that could create family problems. The wife might be viewed as defiant if she participates when her husband had refused. Although the rights of every individual are important and need to be respected, it is also necessary to respect the cultural traditions of others because these traditions govern their everyday lives. Pursuing an ethics of "individual rights" from a non-cultural point of view may lead to other ethical challenges, such as causing conflicts among family members. Additionally, in this case, a man's refusal to allow his wife to participate, combined with the cultural requirement that one should not decline a visitor's requests, places a woman in a difficult dilemma: a woman cannot say "no" to participating in the study because this might be construed as disrespectful to a visitor, and yet she cannot say "yes" because her husband has refused to let her participate.

Another issue relates to building trust. Research assistants faced difficulties obtaining written consent. While some respondents had absolutely no problem with consenting to participate in the study, they did have a problem with signing the consent form. They could not see the point of signing the form after they had agreed to participate; yet, the research assistants still wanted their signatures. This may have been viewed as insincerity on the part of the researchers and possibly evidence of a hidden agenda which was not being revealed. Past experiences have made some people become suspicious of signing documents. Individuals have, for example, lost their land by signing papers, hence their hesitation about signing consent forms.

Researchers working in resource-poor countries may face challenges in obtaining informed consent, particularly in areas where illiteracy is common and where there are different views about the importance of individual consent. In some cases, it may be difficult to determine whether someone truly understands the study goals and risks. Potential research participants may agree to participate because of their poverty, their need for health care, or their beliefs about the importance of respecting or trusting the requests of health workers. An unresolved question concerns what determines the decision to consent—is it the information provided by the research assistants or is it other factors? For the researcher, the assumption is that the decision is based upon the information given; yet, that might not be true.



### **Good practice recommendations**

- Researchers should respect local cultural traditions when conducting a study. It is essential that investigators learn about the social and cultural context before implementing a research project.
- Practices for obtaining informed consent must be sensitive to local cultural context. In some cases, women may need to seek advice or permission from their husband or the head of household before consenting. In other cases, verbal consent may need to be obtained rather than written consent.
- IRBs and ERCs should be educated concerning culturally appropriate methods for obtaining consent from participants in the study population.

## **CASE FOUR**

### **The impact of community dynamics on conducting scientific research in sub-Saharan Africa**

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#### **Case description:**

An international, multicentre, collaborative research project involving researchers and participants from developed and developing countries will be organized to obtain anonymous blood samples from family trios—father, mother and a child aged more than 18 years of age—in communities throughout the world. Blood samples will be transformed into cell lines and stored in perpetuity at a location in one of the developed countries participating in the research. Molecular biologists will use the blood samples to create a new database of human genetic variation. Both the database and the cell lines from which they were generated will subsequently be available for secondary use by any researcher from anywhere in the world, provided that the researcher submits a protocol approved by his/her institution's IRB and the IRB of the storage centre. Such secondary uses of the resource include studies of gene–disease association, pharmacogenomics, and population studies. Funding for all sites, including low-resource countries, was provided by some of the high- and middle-income countries involved in the research, including the component carried out in low-resource countries.

Given the nature of this research, no direct benefit is expected to accrue to the participants in either the developed or developing countries, other than compensation for transportation and lost wages commensurate with the standard of the environment where the study is being conducted. There is no doubt, however, that citizens of developed countries are more likely to be the first to benefit from the outcome of secondary research that may be conducted using this resource. In view of this, as well as the importance of genetic research in general and the risk of population stigmatization, extensive community engagement was planned to educate all participating communities about the research. This was followed by individual recruitment with individual informed consent.

As part of the community engagement process, community advisory boards (CABs) were established. CABs are mandated to provide oversight for all aspects of the study, including community engagement, sample collection, subsequent use of the samples, as well as assessment and distribution of any benefits derived from the study.

At one of the sites in a developing country, a newly democratic nation with equal proportions of Christians and Muslims and where religious tensions frequently lead to civil unrest, the study protocol was followed and the community, at a town hall meeting, nominated seven members, including the chief, to the CAB. The other nominees were community leaders (men and women) representing different religions, and trade and civil associations. The research team nominated two members, neither of whom were members of the community and one of whom was an experienced physician able to guide the committee on medical issues.

At the first meeting of the CAB the board decided to elect a chairman. The closed election was conducted democratically and resulted in the election of a member of the community other than the chief to chair the CAB. Only members of the board nominated by the community voted. The result was accepted by board members and their first meeting proceeded without incident.

At the next town meeting, the chief gave feedback on the activities of the CAB, the election and its result. Many members of the community expressed dissatisfaction with the result of the election and were deeply disturbed about the composition of a committee that included their chief in what they perceived as a subordinate role. Some were also concerned that the newly elected chairman was an

“official” of a particular religion and believed this might limit his ability to mobilize certain sections of the community. In addition, there was concern that he might not be adequately sensitive to the interests and aspirations of members of the community who belonged to alternative cultures and religious traditions. These concerns were so serious that they threatened to halt the research.

The research team came up with an innovative solution that assured the community of the continued supremacy of the chief while respecting the outcome of the election. The chief was made the “chief executive” of the overall study, with responsibility for overseeing all community-related activities associated with the research. The chief would also be consulted in all matters and decisions reached by the CAB. This solution was accepted by members of the community and the study proceeded uneventfully.

### **Primary ethical challenges:**

Teams going into a community to conduct research run the risk of interfering with the community’s power structure and dynamics. In certain instances, this can legitimize unpopular institutions, strengthening the role of institutions that were in decline or enhancing the status of popular ones. Procedures devised for the implementation of research projects may also conflict with the local social, political and cultural practices, and the expectations of members of the community. The latter practices themselves occasionally conflict with standards of democratic choice and representation. Furthermore, in some communities, traditional authorities exist in an ill-defined relationship with modern government structures and institutions. These government institutions may be weak or considered less relevant to community goals and aspirations and may have a history of oppression and lack of responsiveness to the needs of members of the community. In such instances, community members demonstrate greater allegiance and stronger commitment to the protection of traditional institutions—to the extent that they perceive these to be different and responsive to their needs. Researchers need to understand these factors and take them into account when their investigations involve interacting with the community leaders.

In this case, the exercise of democratic rights resulted in an outcome that was not pleasing to the majority who saw it as a “coup d’état” against constituted traditional authority. It is interesting to wonder why the election turned out the way it did, and what this reveals about the feelings of the community elders nominated for the CAB towards the chief, how they understood and exercised their rights to vote, and whether they considered the implication of this choice within their community. There was also concern about representation of the larger community by someone who was intimately associated with a particular religion in a country that had been scarred by religious tensions. Researchers should be sensitive to “fault lines” within communities and be ready to negotiate around them without exacerbating tensions.

### **Good practice recommendations**

- Obtain adequate knowledge about community dynamics and the relevant power structures before conducting a study.
- Collaborate with local researchers who understand the history of the community and its political, social and economic structure.
- Always uphold the core values of representation and democracy in establishing community advisory boards. This builds integrity and trust between researchers and communities.
- Be flexible and creative in exploring solutions when community conflicts arise. Maintain respect for all segments of the community when resolving a conflict.
- Be ready to negotiate community “fault lines” without exacerbating tensions.

## **CASE FIVE**

### **Protecting confidentiality of participants in studies of behaviours that transmit HIV-1 in Russia**

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#### **Case description:**

An epidemic of infection with HIV-1 has inundated Russia over the past six years. The epidemic has been driven primarily by transmission among injecting drug users. This population is marginalized and often harassed by the police, who augment their meagre salaries by extorting money in exchange for not arresting or detaining suspected drug users and sex workers. The speed and magnitude of the epidemic has caught the government, the health sector, and the research community by surprise. As researchers mobilized to understand the dynamics of HIV-1 transmission in Russia, there were no established guidelines for how to conduct research among populations of injecting drug users and commercial sex workers. Most investigators sought ways to protect the participants without appearing to encourage illicit use of drugs. The latter was necessitated by the language of Article 230 of the Russian legal code, which makes "...inducing to use narcotic or psychotropic substances" a criminal offence.

Interpretations of the meaning of the word "inducement" have led to some complex arguments about the legality of any interventions to reduce HIV transmission that are not abstinence-based. Interpretations of "inducement" have also influenced research protocols.

Our research protocol was designed to investigate links between injection risk behaviour, the use of homemade formulations of heroin and methamphetamine, and HIV-1 transmission. This research involved interviewing active injecting drug users in twelve Russian cities. One issue that arose was how to remunerate the drug users who participated in our study. We decided to continue the St Petersburg approach for remuneration, which was providing gifts of food items.

There were two reasons why payments to study participants were made in goods and not in cash, as is the practice in studies of drug users in many other parts of the world. First, the IRB in St Petersburg opposed cash remuneration on the grounds that if money were used to buy drugs, this could place the project in violation of Article 230. Second, cash remuneration might run foul of the Russian tax laws. When grant money is drawn from an organization's bank account, there is no official legal way to pay participants and maintain their anonymity. The payment is viewed as income for participants, which means that full name, address, passport number, tax identification number and pension insurance number must be reported and that the individual and the organization have to pay taxes. This would both violate confidentiality and create enormous bureaucratic burdens. As mentioned above, some studies use monetary payment, and grant money for this purpose is transferred to the personal bank account of one of researchers. But this is not possible for large grants, such as that for our project, which is funded by the United States National Institutes of Health, National Institute for Drug Abuse. Therefore, our protocol called for remunerating study participants with gifts of food including tea, chocolate, milk, and canned goods.

While visiting Khabarovsk in the far east of Russia, we joined with staff of the provincial AIDS centre to travel three hours to Mukhen, a small lumber milling town with approximately 5000 inhabitants. The

town is experiencing an outbreak of HIV-1 infections among its poorer residents, many of whom are drug injectors. Staff from the AIDS centre went to Mukhen one Saturday to provide free HIV-1 counselling and testing at the local clinic. We joined the staff with the intention of interviewing any injecting drug users who came in for testing. We brought with us food items that we had purchased at a supermarket in Khabarovsk and packaged into individual bags each containing food with a value of about US\$ 3.

During the day, we realised that we had inadvertently created a situation that had the potential to violate the anonymity of our research participants. The bags containing the gifts of sugar, tea, meat, and milk that were being given to the interviewees were white plastic bags labelled with a red "HK". By handing out a bag with a bright red label to those we interviewed and restricting the interview only to those who met the study criterion of being an injecting drug user, anyone in the vicinity of the testing site in this small town could readily observe that individuals contacted by the interview team emerged with identical, clearly labelled, plastic bags.

We have no evidence that anyone was adversely affected because they emerged from the clinic carrying the "HK" bag; however, neither did we remain in Mukhen long enough to learn whether there had been adverse events. The potential problem could have been avoided had we employed alternative remuneration strategies. For example, we could have used bags of different colours and designs, which would have reduced the likelihood that a casual observer would be able to identify the holder as an injecting drug user. Alternatively, the problem would not have arisen if we had simply given the study participants a small amount of money that they could easily place in their pockets. The latter option would have violated the study protocol but perhaps would have been more effective in protecting the research participants. But given the tax issues, the former option seems preferable. Providing bags of food to all individuals at the clinic would not solve the problem of protecting confidentiality because everyone leaving the AIDS centre could be identified as someone with HIV/AIDS or concerned about their HIV status.

### **Primary ethical challenges:**

What are appropriate forms of compensation for participation in research? Should an individual's association with a marginalized social group (in this case, injectors of illegal drugs) mandate the form of compensation? How should compensation be modified if the compensation risks compromising participants' anonymity?

The stakeholders involved in this study included, among others, the investigators, the research participants who were recruited because they engaged in an illegal activity, and the institutional review boards (IRBs) of the universities in Russia and the USA sponsoring the study, and the funder. While all the stakeholders may share the desire to further our understanding of behaviours that place injecting drug users at risk for the transmission of HIV, they also may have conflicting social values and concerns. For example, IRBs are charged with the protection of the participants in scientific investigations, yet the interpretation of national and international guidelines for ethical conduct in research varies considerably between IRBs. While some IRBs may disapprove of financial incentives for research participants, other IRBs may consider it to be an appropriate compensation for a participant's time or transportation costs. Moreover, individual IRBs may hold different beliefs about the appropriateness of providing financial incentives to injecting drug users, even if the amount of the incentive is insufficient to purchase drugs or promote drug use. Researchers must receive IRB approval before implementing a study. In some cases, this means that researchers must change study protocols to meet specific IRB requirements. Researchers are not only concerned about achieving successful results, which depends upon effective recruitment strategies; they are also concerned about protecting the confidentiality of their study participants. Injecting drug users participating in a study may be motivated by numerous factors, including a desire to learn more about the prevention of HIV or the incentive provided to participate. Most injecting drug users are also concerned about confidentiality, particularly because they are engaged in illegal activities. Fortunately, there were no incidents involving the police

in this study. Researchers were never asked to disclose information about participants or to open their records for review. In part, this reflects the considerable efforts of the research team to ensure that the protocol was followed in a socially responsible manner.

In this case, there is an inherent tension between the researchers' beliefs about the methods used for remuneration of study participants that would most effectively preserve confidentiality, the IRB's requirement that financial incentives could not be used in this study, and the national tax code.

### **Good practice recommendations**

- Devise strategies for protecting confidentiality that are sensitive to local cultural context and the particular needs of the study population..
- Devise strategies for protecting confidentiality that are sensitive to local cultural context and the particular needs of the study population.
- Educate institutional review boards and ethical review committees concerning appropriate methods to protect confidentiality for the study population.

## **CASE SIX**

### **A study of low birth weight in Madhya Pradesh, India**

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#### **Case description:**

Throughout the world, low birth weight contributes significantly to infant mortality. The central Indian state of Madhya Pradesh is one of the poorer states of India and has one of the highest rates of maternal and infant mortality in the country. Birth weights are not always recorded in Madhya Pradesh, despite government efforts to promote this activity.

This study of low birth weight in infants was conducted in 60 villages in Madhya Pradesh. The main goal of the study was to establish the incidence of low birth weight and factors contributing to low birth weight in this rural population. A retrospective community-based survey of birth weights was done to ascertain the proportion of babies weighed at birth. An exploratory qualitative study was conducted among mothers and traditional birth attendants to understand the social, economic, and cultural reasons for not weighing infants at birth. Both qualitative and quantitative methodologies were used in this study, which had cross-sectional and prospective elements.

#### **Primary ethical challenges:**

A number of ethical challenges were faced by the research team both before the study began and during the course of the study. These are addressed below.

*Transgressing cultural beliefs:* During initial focus groups with mothers, the project team encountered the concept of sutak, which is the pollution ritual associated with birthing. During sutak, the mother and newborn are regarded as “untouchables” and are isolated together away from contact with the rest of the family or community for a period that averages 10–15 days. This ritual is probably an impediment in taking birth weight because none of the local traditional birth attendants or health workers (who are very much a part of the local community) would want to be “defiled” by weighing the child at birth. However, the study protocol required that babies be weighed within 48 hours. The need to weigh the babies soon after birth was in direct conflict with local cultural traditions about appropriate treatment of mothers and newborns. Although the new mothers agreed to have their babies weighed, they may have done so because of their need to acquiesce to the greater social authority of the health workers and research team.

The high rate of infant mortality in the area justified the scientific need for this project. However, in order to meet the study goals, the research team had to talk with participants about personal and sensitive issues related to pregnancy, childbirth and the traditions surrounding these activities. This required maintaining a delicate balance between collecting valid and relevant data and being non-intrusive and culturally sensitive.

*Processes for informed consent:* The women who participated in the study gave verbal consent. Despite explaining the study to them, it is possible that many women may have given consent without understanding the concept of research or the nature of the project. Additionally, being polite to “outsiders” perceived to be in a position of authority is considered to be appropriate behaviour in the study community. Many women may not have felt empowered to decline participation because of a desire to show respect for the researcher obtaining consent. The possibility that the study was not comprehensible to

the women, combined with their need to be polite and their lack of genuine individual decision-making capacity, may have hindered informed and voluntary consent.

Moreover, some of the interviews were long and administered just after the *sutak* period of isolation for mother and baby was over (*sutak* is explained below). Some mothers may have given consent at the beginning of the interview even though they may have wanted to withdraw consent as the discussion proceeded. Research assistants reported that women sometimes gave non-verbal cues indicating they were ready to stop. In this case, researchers needed to be sensitive to both verbal and non-verbal cues given by the respondent and reconfirm consent at different stages of the interview.

*Incentives for study participation:* The research team wanted to provide some form of remuneration to individuals from the local communities involved in the research. After considerable discussion, it was decided to provide a small financial remuneration for the traditional birth attendants who weighed the babies. As per protocol, all traditional birth attendants came to a training session on weighing infants using portable spring balances which they were to be given. However, despite repeated and intense efforts at training, the traditional birth attendants were unable to record weight because they had difficulty understanding the concept of using the balance properly. They were illiterate and had trouble reading the numbers on the scale; although the scale was colour-coded, the study protocol required a record of the exact weight in kilograms. As an alternative, it was decided to train other health workers, called *crèche* workers, to record infant weight with the spring balances. The traditional birth attendants needed to inform the *crèche* workers of the birth immediately so that they could weigh the babies.

The traditional birth attendants were disappointed when they were told that they would not be weighing the babies, particularly since they were expecting a financial incentive for doing this task. To resolve this issue, the team decided to split the incentive between the traditional birth attendants and the *crèche* workers. This created subtle alterations in community dynamics, resulting in competition and “turf battles” between the traditional birth attendants charged with informing the *crèche* workers about the birth of a baby, and the *crèche* workers charged with weighing the infants. It could have been avoided by more sensitive planning and better knowledge of local community resources and capacities.

*Imbalance of power between researchers and participants:* In this international donor-sponsored research project, the research team was of the same nationality as the research participants. Despite this, the power imbalance between the researchers and participants was significant. Members of the research team were from a large urban city, many were men, educated, government employees, and medical professionals. The women participating in the study were villagers, most were illiterate and lacked education. This scenario of imbalance between researchers and individuals involved in their studies is very common in resource-poor settings. Social, economic, and educational differences contribute to the power imbalance and influence the capacity to obtain informed consent effectively,

*Community motivations for participation:* A number of initial visits to the study area were made in which the project team interacted with some of the health workers, mothers and traditional birth attendants in the community. Issues discussed included the goals of the proposed project, its feasibility, the community’s willingness to cooperate and participate, and their views about the study. The local community seemed willing to cooperate, although it appeared that they did not fully understand the reasons for conducting the study. Moreover, the concept of research itself was rather new to this community which had never before been the focus of a research study. However, the community was enthusiastic about the project because of the possibility of resources coming to the area, the opportunity to participate in a “novel” activity, and the arrival of researchers and health workers who were perceived as important and socially powerful.

*Awareness of research ethics:* Although members of the research team had general knowledge of research ethics, a more in-depth understanding of the importance of ethics, and a deeper awareness of subtle ways in which people’s rights can be infringed upon needs to be cultivated. Moreover,



capacity building in the form of resources and training for ethical review of research protocols in this area of India would strengthen the ability of health professionals to conduct ethically responsible studies.

### **Good practice recommendations**

- Informed consent should be sensitive to cultural context. Researchers should consider the participants' capacity to understand the concept of research and the study itself.
- Consent for participation should be periodically reviewed throughout the course of a study.
- Attention should be given to ethical issues arising from the imbalance of power between researchers and participants.
- Incentives and remuneration for participants and others involved in a study should be considered carefully to avoid inadvertent community conflicts that may arise.
- When a protocol demands transgressions of local traditions and customs, alternatives should be considered. If this is not possible, individuals and the study community should be informed and educated about the protocol before implementation.
- Capacity building in research ethics should be strengthened for investigators and local ethical review committees.

## CASE SEVEN

### Evaluating the natural history of *Plasmodium vivax* infection in children in Papua New Guinea

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#### Case description:

The Papua New Guinea Institute of Medical Research (PNGIMR) has been working since 1979 in the Wosera community (East Sepik Province) to develop a malaria vaccine trial site. Malaria is a leading cause of death in many regions of Papua New Guinea. One broad objective of malaria studies conducted in Papua New Guinea is to improve understanding of the relationships between human genetic polymorphism and disease, with the goal of developing more effective approaches to the control and prevention of malaria.

Current research involves conducting a prospective longitudinal study of children in the Wosera area, to document the natural history of *Plasmodium vivax* infection. Although parasite infection is known to vary temporally, in complexity, and in intensity, little is known about the natural history of *P. vivax* infection and subsequent pathogenesis in early childhood. Older children and adults who have been exposed to *P. vivax* will have developed potentially varying levels of immunity in response to the parasite, which may mask an effect of Duffy (*FY*) genotype on susceptibility to *P. vivax* blood-stage infection. Therefore, to assess the effect of differences in *FY* genotype/*Fy* erythrocyte receptor expression on susceptibility to infection with *P. vivax*, the research team is particularly interested in studying younger children (aged 1–24 months), who have had less opportunity to develop parasite-specific immunity. For this study, children will be enrolled from approximately 12 villages and followed weekly for a period of up to two years.

The primary objectives of this study are to determine the mean time to first infection with *P. vivax* and to determine the rate of incidence of infection. The secondary objectives of this study are to assess the impact of recurrent *Plasmodium* infections on child growth, estimate the sensitivity and specificity of blood smear versus PCR-based diagnostic methods for infection with *P. vivax*, and evaluate the effect of the *FY* genotype in children with *P. vivax* malaria.

The study has been approved by IRBs of participating institutions in the USA and Papua New Guinea. Informed consent is obtained from parents of the children participating in the study.

#### Primary ethical challenges:

Ethical challenges that have arisen and continue to confront researchers focus on concerns about the frequency with which blood samples are drawn, benefits to study participants, and the provision of adequate health care for study participants. Strengthening local capacity and maintaining the long history of collaborative partnerships with local researchers and communities remain important concerns.

*Frequency of blood drawing:* The research protocol requires weekly visits with the study team and the fortnightly finger/heel-prick bleeding (200  $\mu$ l, or four to five drops of blood) schedule for the study participants, aged 1–24 months. The rationale guiding this schedule was based upon the two- to three-day cycle for development of the parasite in human erythrocytes. Dynamic changes in malaria infections occur daily. A less frequent monthly bleeding schedule has the potential to miss numerous changes in *P. vivax* parasitaemia and prevalence. Although the study goals and procedures are explained to the parents of the children involved in the study, some families, after agreeing to have their child participate

in the research, are very concerned about the number of blood draws required. Efforts are being made to determine the underlying reasons for parents' concerns and to develop educational approaches to diminish anxiety associated with the weekly visits to have the finger/heel-prick blood draws.

It is important to note that the frequency with which blood samples are drawn required for this protocol might raise concerns for parents in any setting, not only for those in communities in Papua New Guinea. The frequency of blood draws is not a trivial issue. The objectives of the study necessitate the number of blood draws. An alternative would be not to conduct this particular study.

Concerns about the blood draws highlight the need for developing an approach to informed consent that ensures that parents have a clear understanding of the project goals and procedures. Considerable efforts were made to inform and educate communities about the study and to learn about their concerns before starting the project. The research team interacted with local communities informally through social networks and formally at meetings with community members.

*Benefits to the study participants:* Concern has been expressed that there is no direct benefit to the study participants. While studies such as this have the potential to contribute significantly to knowledge of genetic and environmental determinants of malaria, study results provide no immediate benefits to study participants or the communities within which they live. However, the health, growth and development of children enrolled in the study are monitored weekly and prompt feedback on analyses of haemoglobin and malaria blood smear are provided. Access to the health centre is facilitated by four-wheel drive transport when necessary. Moreover, continuous e-mail and telephone contact between PNGIMR scientists and staff with USA-based colleagues help to coordinate analysis of the study's progress, analysis of results, and most importantly, timely feedback to the community about the findings and implications of the study.

*Adequate health care for study participants:* Concern has been expressed regarding the ability of local health-care workers to provide adequate care of the study participants. The study team is coordinated by a nurse practitioner who has been performing malaria surveys within the community for the past six years. The PNGIMR has been conducting studies on malaria in the Wosera community for 25 years. The research team and the community know that it is important to respond quickly to signs and symptoms of malaria. The scientists collaborating on this project from the USA and PNGIMR have and will continue to ensure that adequate supplies of antimalarial drugs (chloroquine and Fansidar—as recommended by the PNG Ministry of Health) are available at the village-based health centres.

*Capacity building and collaborative partnerships:* The malaria research is being implemented in close collaboration with scientists, field staff, community relations officers and, village reporters of PNGIMR. Engaging members of the community as partners, and not merely as participants, emphasizes that the community is making a significant contribution to an improved understanding of an important human disease. Investment in laboratory and other research equipment, and job opportunities for community members.

### **Good practice recommendations**

- Investigators based at multiple international sites should be actively engaged in building collaborative partnerships. This fosters mutual respect and trust between researchers and the study community.
- Prompt and continuous feedback reassures study participants that their participation is appreciated and valuable.
- Respect for cultural traditions builds trust. Researchers should identify concerns that are culturally based and develop strategies for addressing them in a meaningful way.

## **CASE EIGHT**

### **Phase III trial of antibiotics to reduce chorioamnionitis-related perinatal HIV transmission in Malawi**

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#### **Case description:**

This randomized, double masked, controlled phase III clinical trial of antibiotics was conducted in Malawi, and began in 2000. Like many sub-Saharan African nations, Malawi is challenged by considerable poverty, a high rate of infant mortality, and high rate of illiteracy. HIV/AIDS is one of the myriad health problems facing its population. The primary purpose of this study was to determine whether antibiotic treatment aimed at reducing chronic and acute chorioamnionitis would reduce the transmission of HIV from mother to child. The secondary purpose was to determine whether antibiotic treatment reduced pre-term birth and maternal/infant morbidity and mortality. This intervention to reduce the transmission of HIV from mother to child was chosen for evaluation because it has biological plausibility and was very low in cost compared to antiretroviral therapy.

The sample population included 1000 HIV-positive pregnant women recruited from sites in Blantyre and Lilongwe, Malawi. Study participants were randomized to receive either antibiotic treatment or placebo. At each site, about 300 HIV-negative women were enrolled to conceal the HIV status and avoid stigmatization of participating women. All women were aged 18 years or older.

Informed consent was obtained for blood drawing to perform HIV counselling and testing for HIV and routine prenatal testing for syphilis. Women returned to the clinic to receive their test results after one week. Treatment for syphilis, if appropriate, was provided free of charge. If the woman was eligible for the study, an enrolment visit was scheduled at weeks 20–24 of gestation. At the enrolment visit, the study was explained to the woman and informed consent was obtained. The women were then randomized to either the antibiotic or the placebo arm.

Structured questionnaires were administered at enrolment to determine socio-demographic information and background data relevant to HIV/AIDS and sexually transmitted diseases. A routine obstetric examination determined the gestational age. A pelvic examination was conducted and vaginal and cervical swabs were collected to test for sexually transmitted diseases. Blood was drawn to test for vitamin levels and immune status. After these examinations, the first oral “treatment” or placebo was given. All women in both treatment and control arms of the study also received a standard vitamin/mineral preparation daily from enrolment in the study until delivery.

The next study visit occurred between weeks 26 and 30 of gestation. A questionnaire related to medication history and a compliance and pill count were administered. Obstetric and pelvic examinations identical to those performed during the enrolment visit were conducted. A prenatal visit at week 36 was scheduled at which the study treatment or placebo was again distributed in anticipation of labour or the premature rupture of membranes. Since the secondary outcomes included maternal infection and mortality, each woman was asked to continue using the medications after delivery, three times per day, until the 10-day course was completed.

Blood was sampled by heel stick from all infants at age 24–48 hours and at 4–6 weeks. Infants who had a positive result for tests for HIV RNA had reached the primary end-point. Because a second primary end-point included being alive and free of disease at age one year, infants of HIV-positive women who did not test positive for HIV RNA at age 24–48 hours and 4–6 weeks were tested for HIV anti-

bodies at ages 9 months and 12 months, and all who had a negative result were considered to be free from HIV.

The entire duration of the study was approximately three years. For each woman, participation began at 20–24 weeks of gestation and ended at 12 months after the birth of her baby. The overall study period for each woman was approximately 16 months. The infant participation lasted up to 12 months.

All laboratory specimens and records were identified only by a code to maintain subject confidentiality. All records were kept in a locked file cabinet. No appropriate treatments were withheld because a woman was enrolled in this study. Therefore, for example, if a woman had a symptomatic vaginal infection that would normally be treated in Malawi, appropriate treatment was given. Women were reimbursed for their travel time and food expenses to the hospital for the study visits. This was less than US\$ 5 per visit. There was no cost to the study participants.

### **Primary ethical challenges:**

The primary ethical concerns in this case were associated with obtaining informed consent from prospective study participants and standard of care for treating study participants both during and at the completion of the study.

*Informed consent:* The consent procedure for this project was conducted in two phases. Consent was obtained for HIV screening. Once a pregnant woman was identified, shown interest and was eligible, the screening study and the requirements for entry into the main study were explained to her verbally in her local language (mostly Chichewa). The literacy rate among women in Malawi is about 30%; thus, most women were not able to read the consent form. Following the explanation of the study, each woman was asked to verbally explain what would be expected of them, to ensure comprehension. Whether the form was signed or marked, it was only after this screening that the informed consent discussion was considered to be valid. Women who tested positive for HIV, and a subset who were HIV-negative, were asked to participate in the main study at their post-counselling session, when they received the results of their test for HIV. The informed consent procedure for entering the main study was identical to the procedure for the screening phase.

The process of verification used to make sure that the women understood the goals, procedures, risks and benefits associated with the study was viewed by the research team as an important strategy for obtaining consent from prospective participants in this study because many of them had little education and could not read the form. The consent discussion began as a conversation between the woman and a member of the research staff. After the study was explained, another member of the research staff would ask a series of questions to determine adequate comprehension. The form was signed or marked by the woman agreeing to participate, and counter-signed by the research assistant, and later by the principal investigator. However, upon review, the National Institutes of Health Division of AIDS indicated that it would be necessary to have a witness present during the consent discussion and when the individual signed or marked the consent form. Although they complied with this request, the research staff were concerned that this would present an awkward situation since the “witness” would be a third party—and a silent party—in what they viewed as a conversation that required discretion and trust. In this cultural context, persons with HIV are sensitive about their status. A confidential and respectful conversation, one that did not involve a third person, was considered by the researchers to be appropriate for obtaining consent, particularly since a process for assessing adequate comprehension had been devised.

*Standard of care:* The University of North Carolina IRB reviewing this study expressed concern about standard of care and the use of a placebo. When the study began, nevirapine was not available in Malawi for routine antenatal use by HIV-infected women, and there were no immediate plans to initiate use of nevirapine. In spite of the success of a shorter nevirapine regimen in Thailand, the cost was high (about US\$ 80 per woman) which was and is prohibitive in Malawi and in all of sub-Saharan Africa.

At a meeting sponsored by the Pediatric AIDS Foundation and Emory University in the late 1990s, experts recommended, “There is a need to evaluate simple and feasible interventions other than anti-retroviral agents for their efficacy in diminishing HIV mother-to-child transmission in developing nations.” They also noted that “in the study of non-antiretroviral interventions (e.g. vaginal lavage or antibiotic treatment), a “no drug” intervention control design may be justified ethically in a setting where antiretroviral therapies are not generally available to any individuals in the community.” They recommended that successful simple measures that are affordable and sustainable should be included as part of the standard care in developing countries with limited resources. Therefore, recently proven beneficial therapies such as testing and treatment for syphilis and multivitamin supplementation during pregnancy were provided to all women. In fact, the use of vitamin supplementation during pregnancy is not the standard of care in Malawi. If the benefits of this study are realized, then women in Malawi and other resource-poor countries, especially in sub-Saharan Africa, would be able to implement an affordable strategy to reduce HIV vertical transmission.

During the course of the study, antiretroviral therapy became more available in Malawi through a national programme set up by the Global Fund to Fight AIDS, Tuberculosis and Malaria to provide access to the drugs. Although the researchers did not have sufficient funds in their budget to secure the drugs necessary to treat their participants, all HIV-positive women and their HIV-infected babies were referred to this programme. This programme created opportunities for effective treatment—once it was available—for women and their babies both during the study and at the study completion.

### **Good practice recommendations**

- Researchers should be creative in designing strategies to ensure adequate comprehension of study goals, procedures, risks and benefits when obtaining informed consent. This may include educational interventions before consent, or discussions after consent that provide researchers with a method for determining whether individuals understand the nature of the research.
- Researchers must consider appropriate standards of care in the design and implementation of an investigation, including provision of therapy to the study population when the research is complete. Researchers must be ready to change the research design if existing therapies become available in an area where previously study populations were denied access.
- Researchers should make every effort to identify avenues for securing the best possible treatment available for study populations. This means that researchers may need to work collaboratively with funding institutions, governmental agencies, and pharmaceutical companies in developing suitable strategies to secure therapy for participants.

## CASE NINE

### **Ethical review of epidemiological health studies in Pakistan: responsibilities of researchers for medical care of participants**

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#### **Case description:**

Epidemiology researchers traditionally have not been responsible for providing medical care for their study participants or the communities within which they live. Moreover, budgets are limited and investigators are constrained by the resources available from funding agencies. In the context of resource-poor settings in particular, this presents ethically challenging issues. Should these researchers take on greater responsibility for the provision of medical care or for capacity building in relation to the health-care infrastructure of study sites? The following two cases call attention to these issues and the questions raised by an ethical review board (ERB) in evaluating them.

*Case 1:* An epidemiological study, designed to estimate the burden of *Shigella* dysentery in slums of an urban area in Pakistan was presented to an ethical review board (ERB). The protocol indicated that all patients in the specified location who had diarrhoea would have stool cultures; if stool specimens were not available, anal swabs would be taken. Walk-in or less sick patients with simple diarrhoea would receive advice regarding the use of oral rehydration therapy. Those with bloody diarrhoea would be given Nalidixic Acid as per WHO guidelines. Patients who were very sick and severely dehydrated would be referred to the nearby hospitals after taking the required specimens.

The ERB informed the researchers that there was no public sector hospital in the study area and that the quality of medical care was not reliable in small private clinics or smaller “hospitals.” The ERB suggested that impoverished individuals participating in the study should be treated at the hospital with which the researchers were affiliated, and that the cost of treatment should be built into the research budget. Alternatively, the ERB suggested that researchers should arrange for treatment in nearby professional clinics. The researchers reminded the ERB that investigators were not responsible for providing medical care in epidemiological studies. One researcher said, “If we go by your assertions then tomorrow in a seroprevalence study of hepatitis B, do you expect us to treat all patients found to have hepatitis B disease and immunize all those who do not have the disease?” Eventually, the researchers agreed to provide treatment for the very sick patients.

*Case 2:* Another study planned for northern remote areas of Pakistan was presented to the ERB. In this protocol, study participants included children aged under five years with pneumonia and meningitis. During winters there is a high rate of mortality from these diseases because of their high incidence and the inability of the patients to access health care in remote areas. The study was designed to investigate the common causative organisms that could be involved in the etiology of these diseases. If etiology is proven and the incidence of these diseases significantly high, the ultimate objective is to make a case to government authorities to include meningococcal, pneumococcal and haemophilus vaccines in primary immunization programmes. Researchers planned to collect sputum specimens, throat swabs and samples of cerebrospinal fluid, depending on the clinical diagnosis. Researchers would provide some medical treatment for patients suffering from these diseases. The parents of the children would be counselled and provided with simple oral, first-generation antibiotics. Children who were more seriously ill would be referred for medical advice at local primary health-care centres or the nearest hospital. The ERB noted that primary health care centres and hospitals in these remote areas were

either non-existent or provided inadequate medical care; in many cases, appropriate medicines would not be available to individuals at these centres.

This study was initiated by researchers from a university in the USA and their local collaborators. The study had been approved by the IRB at the institution in the USA and was now under review by the local collaborators' ERB. When the ERB raised the issue of providing treatment to very sick children, the researchers were very annoyed and suggested that ERB members were obstructing important and vital research. They also questioned the credentials of individuals sitting on the ERB. The researchers claimed that this was an epidemiological study and they neither had funds to provide medical treatment nor was it their responsibility to treat individuals participating in their studies. The ERB noted, however, that the researchers planned to fly expensive laboratory equipment to these remote areas and train personnel in collection, storage and testing techniques. Moreover, researchers from the locality and from the USA were to fly in and out to supervise staff at the study sites. Resources for these activities were all provided for in the budget, while medical treatment for study participants was not.

When the ERB did not change their position on this issue, the researchers flew in to meet with the committee. After long and acrimonious discussions, the researchers agreed to provide injectable third-generation cephalosporin, which was the standard of care for very sick children. At a later date, the same researchers submitted a new protocol for a study of measles vaccine. This time, the ERB asked researchers to strengthen and develop the local general practitioner referral system via which children with measles would be treated. The researchers promptly withdrew their protocol. Subsequently, ERB members learned that the same study was being conducted through a different institution, one with an ERB that was known to "rubber-stamp" research protocols.

### **Primary ethical challenges:**

While there has been increased discussion of ethical issues surrounding the implementation of clinical trials, there has been less attention to the obligations of epidemiology researchers to individuals and populations involved in their studies. Epidemiological research is vital for documenting health statistics and developing preventive health measures for both industrialized and developing countries. However, individuals participating in epidemiological research in developing countries, particularly in remote rural areas, do not have access to health care as they would in industrialized countries. Lack of access to medical care, or the availability of any health care, raises a number of thorny issues and questions:

- Should researchers be responsible for providing medical care to participants in epidemiological studies, especially in the context of resource-poor settings?
- Researchers conducting epidemiological and public health studies—like other investigators—face budget constraints. These studies are vitally important because they provide data relevant for the health-care needs of populations. Is it feasible—or even ethical—to expect researchers to treat study participants or to provide support for building local health-care infrastructures? The consequences of requesting greater responsibility for the provision of medical care might result in fewer available resources for collecting health statistics and documenting important information on the determinants of disease.
- Should epidemiological studies only be allowed if they are linked with definite intervention plans at the conclusion of the study?
- Is it right to have greater expectations of externally funded and sponsored research than of poorly funded and desperately needed indigenous research?
- What should be done if the external collaborating institution (from a resource-rich country or from private industry) threatens to take research to another local institute where ERBs do not exist or where protocols are "rubber-stamped"?



- Is it right for the ERBs to ask for budgetary details and the details of sponsors in epidemiological studies? In case 2, for example, is the vaccine industry pushing for the use of their vaccine in immunization programmes, and if so, is this wrong?

Researchers alone should not necessarily be held responsible for the adequate provision of medical care to study participants. More active and collaborative engagement in developing strategies to reduce health disparities is needed on the part of private and public funding institutions, governmental agencies, and the global pharmaceutical industry. However, it is time to seriously consider the obligations of researchers to provide care for study participants, and the obligations of ERBs and IRBs to expect protocol changes that require the incorporation of medical treatment for individual participants or communities.

### **Good practice recommendations**

- Researchers should make every effort to devise strategies for the provision of medical treatment for study participants when it is appropriate.
- Capacity building should be a priority for researchers working in resource-poor settings.
- Ethical review boards and institutional review boards should be strengthened, especially in resource-poor countries, in order to avoid the problem of “rubber-stamping” questionable research protocols.
- Collaborative partnerships should be developed between researchers, funding agencies in public and private sectors, governmental agencies, and private industry to seriously consider methods for reducing health disparities that exist between resource-rich and resource-poor communities.

## CASE TEN

### Research and employment opportunities in resource-poor settings

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#### Case description:

Tropical disease research is concentrated in resource-poor areas of the world where employment opportunities are limited, especially for women with less education and formal training. The establishment of field-based operations research creates employment opportunities that may be difficult to sustain after the project ends, leaving a staff of skilled workers bereft of income or work prospects. In such contexts, what are the implications for investigators who introduce the employment opportunities? What obligations, if any, do researchers have to ensure the continuity of employment for project staff in communities of economic hardship?

Our case study is drawn from a five-year intervention to improve the quality of life for women with lymphatic filariasis in Haiti. The project achieved success in many areas and at its completion employed a staff of 24 women. Despite planning for the end of funding and facilitating a transition to local management, the loss of employment triggered heated conflict within the group and even resulted in death threats between opposing factions. The experience led us to ask ourselves, could this have been prevented?

The research programme began in 1998 as a pilot project funded by the WHO/TDR Gender Sensitive Interventions initiative. The intervention involved organizing peer support groups for women with lymphedema and elephantiasis in the commune of Leogane, Haiti. Six women were recruited from the patient population of the local hospital-based filariasis treatment programme. This phase of the project lasted two years, and was expected to end in 2000. However, the intervention attracted the attention of other funding agencies and we were given an opportunity to expand and extend the support group programme into 2003 with financial assistance from the Presbyterian Church USA. This extension of funding was a double-edged sword: it allowed more people to benefit from the programme and at the same time the continuation of funding created an expectation that somehow new funding could be found to prolong the programme indefinitely. This did not happen, despite our best efforts, and staff were laid off in December 2003. Only two employees were retained for a limited seed project begun in another part of the country.

As the reality of unemployment set in, a historical milestone and charged political atmosphere in the country fuelled intense emotions and frustration among the former staff members. While Haiti celebrated the 200th anniversary of its independence wrought through violent rebellion, protests and demonstrations raged throughout the country in the early weeks of 2004. In February 2004, President Jean Bertrand Aristide was ousted from office and a multinational peacekeeping force entered the country to restore order. At the local level, in-fighting within the former support group staff members reached a peak, after months of factionalism, accusations, threats between family members and acting out in the streets. Illnesses and misfortunes among the former employees were suspected as malevolent in origin, possibly the workings of jealous colleagues. During a site visit in February, 2004, the staff members pleaded passionately with the researchers to find some way to continue their salaries—they were willing to do anything for pay. “How will I be able to take care of my children without work?” they asked. Family members of one faction publicly threatened the opposing faction with death.

At this point we became very worried that our successful project would end in tragedy. Steps were taken to diffuse tensions among the parties involved, and ongoing efforts to develop a micro-enterprise project with programme participants were suspended because of group tensions. At the time of writing, we are still seeking ways to provide employment for the former staff members. No one has been harmed, but hard feelings and intense disappointment remain. Furthermore, there was a strong sentiment among the former women staff members that male workers in other filariasis-related programmes in the community had benefited more from their work experience, leading to other opportunities for employment or educational advancement. In contrast, the women who lead the support groups for other women, they pointed out, have not realized comparable benefits.

### **Primary ethical challenges:**

In recent years, ethicists have begun to consider researchers' obligations to study participants and communities at the end of a project. Concerns have centred on obligations to provide continued access to medical treatment or drug therapies. Ethical questions surrounding obligations to assist in the creation of job opportunities for local research staff have not been adequately addressed. Difficult questions arise when economic opportunities are created for people living in extreme poverty. Is creating a sense of relative deprivation a harm that should be anticipated and weighed in the assessment of risks associated with research? Did we fall short of our obligations as ethical researchers in this situation? These are questions worthy of discussion, even if there is no clear answer to the issues raised. Our study calls attention to the impact of research on existing community dynamics, particularly in relation to employment opportunities and competition for jobs in impoverished areas. These issues often affect women disproportionately in areas with high unemployment. Additionally, the study highlights the implications for providing training and education for research staff who may not be able to find comparable employment when a study ends.

### **Good practice recommendations**

- Promote capacity building for staff training and education and strengthening the local health infrastructure.
- Make efforts to provide for the continuation of effective research interventions and programmes.
- Make efforts to assist in job transitions for staff at the completion of a study.
- Identify strategies for diffusing staff tensions associated with the loss of employment at the end of study.
- Before initiating a study, consider carefully the potential for conflicts that may occur within communities and among staff when a project is completed.
- International and national guidelines for ethical conduct in biomedical and behavioural research should consider questions associated with obligations of investigators to provide employment opportunities for staff when a project ends.



## 5. RECOMMENDATIONS

Debates among health professionals, policy-makers and the public concerning the application of guidelines for ethical conduct in health research conducted in developing countries are likely to continue as new information becomes available. Researchers in biomedicine, public health, and the social and behavioural sciences confront the challenging task of adhering to national and international regulations in social and cultural environments in which ethical guidelines may not be easily translated or applied. Increased awareness of ethical concerns associated with study design and informed consent among researchers working in resource-poor settings is needed. But strengthening professional knowledge about international research ethics is not enough. Investigators need practical advice on the best methods or models for articulating ethical guidelines in the field. Empirical research on a wide range of issues relevant to the application of ethical guidelines is needed, including studies of macro social and economic developments that drive the globalization of the biomedical research enterprise. Technological and financial resources are also necessary to build capacity for local collaborators and communities to ensure that results of research are integrated into existing health systems. This requires collaborative efforts and engaged commitment on the part of investigators, funding agencies, policy-makers, governmental institutions, and industry.

### 5.1 Recommendations for good practice

Listed below are recommendations for researchers and policy-makers concerned about ethical practices for research design and informed consent in multinational studies conducted in resource-poor settings.

- **Respect the cultural traditions of study populations and communities**

Researchers should respect local cultural traditions when conducting a study. It is important that investigators learn about the social and cultural context before implementing a research project. Respect for cultural traditions builds a foundation of trust between researchers, study participants and the local community. Researchers should identify concerns that are culturally based and develop strategies for addressing them in a meaningful way. When protocol procedures require a transgression of local traditions and customs, investigators should initiate discussions with local leaders and local ethics committees to seek their advice on developing alternative methods for achieving successful results. In all cases, individual participants and the study community should be well informed and educated in a culturally and linguistically appropriate manner about the protocol before implementation.

Incentives and remuneration for participants and others involved in a study should be evaluated in light of the socioeconomic and cultural context. Strategies for protecting confidentiality should be sensitive to local cultural context and the needs of the study population. Studies examining particular health problems may require specific knowledge of local cultural and behavioural practices that are relevant to the issue. For example, conducting research on HIV prevention in culturally diverse settings requires local knowledge about gender roles and the negotiation of sexual activities.

- **Strengthen capacity for developing collaborative partnerships**

Collaborative partnerships must be strengthened between researchers in resource-rich and resource-poor settings. Building strong collaborative partnerships fosters mutual respect and trust between researchers and the study community. This requires the active engagement of investigators based at multiple international sites.

Capacity building should be a priority for researchers working in resource-poor settings. Local health authorities and civil society should make efforts to strengthen the local health infrastruc-

ture and to provide for the continuation of effective research interventions and programmes. Sponsors and funders of research should also promote capacity building by providing resources for technical support and staff training and education. Efforts should be made to assist in job transitions for staff at the completion of a study.

Collaborative partnerships should be developed between researchers, funding agencies in public and private sectors, governmental agencies, and private industry to seriously consider methods for reducing health disparities that exist between resource-rich and resource-poor communities.

- **Strengthen education in research ethics for investigators**

Ethical conduct in biomedical and behavioural research requires investigators to be sensitive to the moral dimensions of study design and implementation. Yet, in many settings, educational opportunities in research ethics are often inadequate or non-existent. Training in research ethics should be strengthened for investigators in both resource-poor and industrialized nations, particularly when studies involve participants from communities with poor or low literacy.

- **Strengthen capacity for independent ethical review of protocols**

Ethical review of research protocols in resource-poor settings should be improved. Capacity building should include greater access to educational opportunities in research ethics for members of IRBs and ERCs. IRBs and ERCs in both resource-poor and industrialized nations should be educated concerning culturally appropriate methods for obtaining consent from individuals participating in international studies and appropriate methods to protect confidentiality for study populations. Particular attention should be given to the need to be cognizant of cultural differences in reviewing protocols for collaborative research. Additionally, responsibilities of multiple IRBs and ERCs involved in a single project must be clarified to avoid confusion. Finally, regulation of ethical review of clinical trials by private companies from resource-rich countries is needed.

- **Develop culturally meaningful approaches to informed consent**

Researchers should develop culturally appropriate methods for obtaining informed consent. Recently, Woodsong & Karim (2005) developed a critical model designed to enhance and strengthen the process of informed consent for research in diverse settings. The framework they outline considers both individual and community concerns and is focused on three stages: pre-enrolment, enrolment, and post-enrolment. Although Woodsong & Karim base their model upon their experiences with the HIV Prevention Trials Network, it has broad applicability for biomedical and behavioural research implemented in any international context.

In some settings, sensitivity to local cultural context requires that investigators provide opportunities for individuals to seek advice or permission from a third person, such as a spouse or head of household. In some cases, researchers may need to consult with local community leaders before implementing a study. In every situation, researchers should pay attention to ethical issues arising from the imbalance of power between researchers and participants. The social position of study participants influences their capacity to provide voluntary consent. Power inequities diminish the potential for voluntary consent. Special consideration should be given to groups who are stigmatized or marginalized because of their social activities, political affiliations, or because they suffer from a particular illness.

Informed consent documents should use language that is simple, clear, and linguistically correct. Translations of documents must adequately represent local dialects. Appropriate methods for back-translation should be employed when necessary.

Efforts should be made to insure that participants fully understand the implications of participating in a research project. In developing approaches to informed consent, researchers should consider participants' capacity to understand the concept of biomedical or behaviour research. Researchers should be creative in designing strategies to ensure adequate comprehension of study goals, procedures, risks and benefits. This may require implementing educational interventions prior

to consent or developing methods for determining an individual's comprehension of the study objectives. For example, participants may be provided with information about the research in pre-counselling sessions. The use of graphics and pictorial images may reinforce participants' understanding. In some cases, researchers may implement verbal or written evaluations to verify comprehension of the elements of informed consent. Investigators might consider conducting focus groups with community members before implementing a study, to better understand issues associated with the preparation of consent forms and the development of approaches for obtaining consent. In all cases, informed consent documents should be pre-tested with individuals representing the study population.

Informed consent is a dynamic and interactive process of communication to ensure voluntary and informed participation; it is not simply the request for a signature or thumbprint. If relevant, consent for participation should be periodically reviewed throughout the course of a study.

- **Use appropriate documentation for the consent form**

Investigators must carefully consider the need for verbal or written documentation of consent for research and culturally appropriate strategies for witnessing the consent discussion. Researchers should be sensitive to individuals who may be illiterate, who may not understand the need for a signature or thumbprint on the consent form, and who may have experienced past abuses that resulted from placing their signature on what appeared to be a "legal" document. Strategies to reduce anxiety about the documentation of the consent process should be developed.

- **Apply appropriate standards of care and provisions for medical treatment**

Researchers must consider appropriate standards of care in the design and implementation of an investigation. Investigators must be ready to change the research design if existing therapies to which study populations were previously denied access become available in an area. Researchers should work collaboratively with funding institutions, governmental agencies, and pharmaceutical companies in developing strategies to provide effective therapies for participants during the course of a study and, if relevant, after a study has ended.

- **Provide ongoing feedback to the study participants and community**

Prompt and continuous feedback reassures study participants and their community that their participation in a research project is appreciated and valuable. Researchers should develop plans to disseminate information about the study and its results in ways that are culturally and linguistically meaningful. Local collaborators or members of a CAB, if one has been established, should be helpful in advising researchers on the best methods for providing feedback during the course of a study and after its completion.

- **Develop plans for resolving conflicts surrounding research implementation**

Researchers should carefully consider the potential for conflicts within the community that may occur during the course of the study or at its completion. This requires investigators to obtain adequate knowledge about community dynamics and existing power structures before conducting a study. Often, conflicts may not or cannot be anticipated. When they happen, researchers should be flexible and creative in exploring all possible solutions. Every effort should be made to show respect for all segments of the community when resolving a conflict. In some situations, particularly in impoverished areas, the end of a project means the loss of crucial employment for community members. Researchers should identify strategies for diffusing staff tensions regarding the loss of jobs at the end of study. As mentioned above, assistance should be provided to secure ongoing employment for local research staff.

## 5.2 Recommendations for research on research ethics

There continue to be gaps in existing knowledge regarding the application of national and international ethical guidelines for research with study populations and communities in resource-poor settings. Greater attention should be given to the development of theoretical approaches and analytical tools for assessing social and ethical challenges to planning and implementing biomedical and behavioural studies in developing countries. Descriptive empirical research is needed to determine normative behaviour and to promote the development of new ethical guidelines or revisions of guidelines that have been established.

What should be the focus of future research on social and ethical challenges associated with study design and informed consent in resource-poor settings throughout the world? Possible directions for research on a range of issues are identified below.

- **Informed consent**

There is an urgent need for strategies to improve informed consent discussions so that comprehension of study goals and objectives is enhanced in all cultural settings. There is substantial anecdotal evidence concerning challenges to informed consent and, in recent years, empirical research on informed consent practices has increased. Nevertheless, there is a need for more systematic empirical investigations on voluntary participation and informed consent practices for research conducted in resource-poor settings.

Future studies should include assessments of how language, literacy, beliefs about decision-making authority, and beliefs about the nature of research influence voluntary participation and comprehension of information. Moreover, it is vitally important that educational interventions to improve consent for biomedical and other health-related research be developed and tested for linguistically and ethnically diverse populations in resource-poor settings. Additionally, there is a great need for studies examining modified or simplified approaches to informed consent for research. Specifically, simplified methods for obtaining consent should be designed and tested to minimize the challenges associated with informed consent and maximize the potential for comprehension of difficult scientific concepts for study populations in resource-poor settings.

- **Community consultation for research**

Empirical research is needed on the process of community consultation for approval or permission to conduct a study. Researchers should consider how cultural, social, and political factors influence decision-making among individuals representing the local population. How do leaders derive their authority to speak for the community? Who are they representing among community members? Are all segments of the population represented by their authority or are the interests of some segments of the community marginalized or neglected? How is the community informed about the results of the consultation? What are the implications of community consultation for expressions of individual autonomy, voluntary participation, and informed consent?

- **IRBs and ERCs**

Future research should address the constitution and decision-making processes of IRBs and ERCs in both industrialized and resource-poor settings. Strategies for strengthening their capacity to effectively and fairly evaluate research protocols for multinational studies in developing countries should be explored. How are the members of IRBs and ERCs chosen? What is their experience or professional training and how is this relevant for ethical review of protocols? How do IRBs and ERCs interpret and apply national and international guidelines for ethical conduct in research? Do applications of guidelines differ depending upon the nature of the study, the researchers involved, the study sponsorship – whether it is funded locally, by an international governmental agency, or by a multinational pharmaceutical company? Special attention should be given to the social and political dynamics that influence the “gate-keeping” function of review committees which, in ideal circumstances, serves to protect study populations, but conversely, may also contribute to the exploitation of vulnerable populations.



- **Collaborative research partnerships**

More information is needed on the nature and conduct of existing collaborative partnerships between researchers from resource-poor and resource-rich environments and effective strategies to strengthen these partnerships. What are the factors that contribute to a strong foundation for building collaborative partnerships between researchers from industrialized countries and those from developing countries? What resources are necessary to sustain a long-term collaborative partnership? How can researchers, academic institutions, private and public funding agencies, governmental authorities, and the biomedical and pharmaceutical industry work cooperatively to ensure that resources are available for effective collaborative partnerships? How can these diverse groups work together so that the benefits of research results are available for study populations and local communities in resource-poor environments?

- **Development of instruments to study ethical challenges in research design and implementation**

Survey questionnaires, interview schedules, and other instruments should be developed, tested, and validated for examining a range of factors that influence ethical challenges in research design and informed consent. Instruments to explore individual and community identity, beliefs about the process of decision-making for participation in biomedical or behavioural studies, and past experience with scientific research would be particularly helpful. Investigators could apply these research tools in the context of conducting formative research for the design of clinical trials or other biomedical and behavioural studies. These instruments could also be tested and validated as primary investigational tools in studies of the influence of social and cultural factors on ethical challenges surrounding research design or informed consent practices in ethnically and linguistically diverse multinational settings.

Robust empirical accounts of cultural, social and moral issues surrounding research design and informed consent must include not just an assessment of local beliefs about the nature and conduct of investigations, but also the broader social and political factors that influence and transform the globalization of biomedical and behavioural scientific initiatives.



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