



# postnote

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## RESEARCH ETHICS IN DEVELOPING COUNTRIES

The UK funds an increasing amount of biomedical research in developing countries. Research proposals are reviewed by research ethics committees, usually in both the UK and the countries where research is to take place. Exact ethical requirements vary according to national policy, funding body and research institution. A key international document on research ethics, the Declaration of Helsinki, will be revised in 2008. This POSTnote describes the types of research conducted in developing countries, the ethical review process and the arising issues.

### Background

Biomedical research seeks mainly to develop new drugs, vaccines and medical techniques and to improve public health systems. It often involves human participants, as in genetic sampling or clinical trials. In developing countries, where infectious diseases cause half of all deaths,<sup>1</sup> biomedical research targets include HIV/AIDS, tuberculosis, malaria and diseases that have received limited attention in the past, like sleeping sickness and dengue fever.<sup>2</sup> UK funding for this research comes from three main streams (see Box 1):

- **public sources**, including the Department for International Development (DFID) and the Medical Research Council (MRC);
- **medical charities**, such as the Wellcome Trust;
- **private sector** pharmaceutical companies.

### Ethical review policies and procedures

There are numerous international and national guidelines (see Box 2) on research ethics. Many consider the World Medical Association's (WMA) Declaration of Helsinki to be the most influential.<sup>3</sup> According to the Declaration and other documents, all medical research projects involving human subjects should undergo ethical review. This is

### Box 1. Examples of UK-sponsored research

#### Department for International Development (DFID)

DFID contributes to a variety of programmes. These include several product development public-private partnerships: the International Aids Vaccine Initiative (£20m, 2005-08), the International Partnership for Microbicides (£8.7m, 2005-08), the TB Alliance (£6.5m, 2005-08), the Medicines for Malaria Venture (£10m, 2005-10) and the Drugs for Neglected Diseases Initiative (£6.5m, 2005-08).

#### Medical Research Council (MRC)

The MRC Laboratories, in The Gambia are the UK's largest single investment in medical research in a developing country (£41.6m, 2006-11). Staff work on HIV/AIDS, tuberculosis, malaria and other tropical diseases. A second research unit in Uganda is based at the Uganda Virus Research Institute and focuses on HIV/AIDS (£15.3m, 2006-2011).

#### The Wellcome Trust

The Trust funds major research programmes in South-east Asia, Kenya, Malawi and South Africa, focusing on diseases such as dengue, typhoid, HIV/AIDS, tuberculosis and malaria, (total funding in developing countries: £203.5m, 2003-2007).

#### Private sector

Pharmaceutical companies such as GlaxoSmithKline<sup>4</sup> and Pfizer<sup>5</sup> support public-private partnerships working on drug discovery for HIV/AIDS, tuberculosis, malaria and previously neglected diseases, through research, funding, training and sharing medicinal compounds.

usually carried out by an institutional or independent local research ethics committee (REC) or by a national ethics committee. A REC will generally expect a research proposal to demonstrate:

- how informed consent (see later sections) will be obtained from all research participants;
- that confidentiality will be ensured;

- that potential harm to participants will be minimised;
- the scientific validity of the project (sometimes also assessed by a separate committee).

### Box 2. Research ethics regulation and policies

Numerous legislative and guidance documents on research ethics exist, at international, national and institutional levels.

#### Legislation

Legislation affecting researchers in the UK includes the EU Clinical Trials and Good Clinical Practice Directives (2001 and 2005) and the UK Medicines for Human Use (Clinical Trials) Regulations (2004, amended 2006).

#### International guidance

Documents include the World Medical Association's Declaration of Helsinki (2000), which sets out ethical principles, as well as regulatory instruments such as the Good Clinical Practice guidelines of the World Health Organisation (1995) and the International Conference on Harmonisation (1996). The Council for International Organisations of Medical Sciences has produced guidelines outlining how the Helsinki declaration can be applied in developing countries. The United Nations Educational, Scientific and Cultural Organisation adopted the Universal Declaration on Bioethics and Human Rights in 2005, to assist member states in the formulation of national legislation, regulations or policies.

#### National guidance

The Medical Research Council and the Wellcome Trust in the UK have each produced ethical guidelines on research in developing countries. The Nuffield Council on Bioethics' report, *The Ethics of Research Related to Healthcare in Developing Countries* (2002, followed up in 2005), is also frequently referred to by researchers and RECs in the UK and in many other countries. Several institutions in developing countries have also produced ethics documents, including the Indian Council of Medical Research and the Kenyan National Council for Science and Technology.

For research in the developing world there are further considerations. These include: which legislation or guidance should be followed; whether RECs have sufficient capacity and expertise; how informed consent can be obtained; and how projects will relate to and meet participants' needs.

## Policy context

### UK and EU regulations

The UK's Medicines for Human Use (Clinical Trials) Amendment Regulations (2006) specify that clinical trials must be conducted in accordance with the WMA Declaration of Helsinki and the EU Directives on Clinical Trials and Good Clinical Practice. Several stakeholders have sought guidance on whether these requirements apply to trials sponsored by or conducted through UK-based funders, pharmaceutical companies and institutions but that take place in developing countries. Some interpret them as clearly applying only to trials carried out partly or wholly within the EU. Others would like further clarification on this issue.

The Declaration of Helsinki was last revised in 2000, but the Medicines for Human Use Regulations cite the 1996 version. In 2008 the Declaration is being revised again. The UK's input into the revision process is being co-ordinated by the British Medical Association. A collective response to the first draft, from bodies such as the

Department of Health, the MRC, the Nuffield Council on Bioethics and the Wellcome Trust, was sent to the WMA in early 2008. One concern is that the WMA appears to be seeking to expand the scope of the Declaration. A second draft will be released for further comment in May 2008 and the final version will be adopted in October 2008. The likely impacts of any revisions are as yet unknown, as it is uncertain whether other international and national documents that draw on the Declaration will follow suit.

### Multiple sources of guidance

Research ethics guidelines operate at international, national and institutional levels (Box 2). Opinions differ on how far this proliferation<sup>6</sup> of documentation is a problem. Some ethicists and researchers appreciate being able to draw on different perspectives on how to deal with the issues outlined below. They consider a 'one size fits all' approach inappropriate, as research is carried out in different social, cultural and economic contexts. Others find the range of guidance confusing, particularly on the 'standard of care' debate (see Box 3). They would prefer the different sources to be streamlined both nationally and internationally. Oxfam advocates the World Health Organisation's Good Clinical Practice guidelines as a viable universal standard.

### Box 3. The 'standard of care' debate

Standard of care refers to the nature of care and treatment provided for research participants.<sup>7</sup> The Declaration of Helsinki (2000) states that new interventions should be tested against the 'best current' preventative, diagnostic or therapeutic methods. This is sometimes interpreted as requiring a 'universal standard of care': the best current treatment available anywhere in the world. The results of a clinical trial testing a new intervention against this standard would be of little relevance in countries where such treatments are usually unavailable. Hence many researchers, ethicists and pharmaceutical companies endorse the best treatment available nationally as a minimum standard of care, seeing a universal standard as liable to preclude important research. The Council for International Organisations of Medical Sciences accepts that the best current intervention may not be available locally and permits an 'established effective intervention' to be used instead.

## Ethical review

Most guidelines require that ethical review should be carried out in the country where the research is to take place. Where research is conducted in collaboration with a UK institution (as is mandatory for MRC-funded research overseas, for example), review by a UK-based REC is also usually required. For multinational research projects this may involve several different ethics applications. The various RECs involved may hold contrasting views on whether or not a project can be approved, particularly if working to differently nuanced guidelines. The Nuffield Council on Bioethics advises that such disagreements should be avoided or resolved through dialogue.<sup>7</sup> This rarely takes place, however, so that researchers find themselves going back and forth between committees, often over relatively small issues. Some ethicists see this as a missed opportunity for an educational exchange of views between members of RECs working in widely varied contexts.

### Developing local ethical review capacity

Developing countries vary considerably in their abilities to carry out ethical review of biomedical research. Some have longstanding systems in place, while others are only now beginning to establish them. MalariaGEN (see Box 4), a large multinational research network, found that it needed to engage actively with some RECs in Africa and Asia to ensure appropriate review procedures. Some of the problems RECs might face include:<sup>8</sup>

- heavy workloads, where there are too few RECs to deal with growing numbers of research projects;
  - recruiting sufficiently diverse memberships (RECs are generally expected to include scientists, ethicists and lay persons from different backgrounds and genders);
  - ensuring decisions are made independently of governmental, institutional and financial interests;
  - making decisions on new, complex research that poses ethical dilemmas, such as genetic research;
  - lack of mechanisms for quality assurance and avenues of redress for researchers;
  - high running costs, especially for project monitoring.
- Some RECs charge for ethical review. To avoid this being seen to compromise committee independence, the Nuffield Council suggests that fees could be paid into a central fund for training and development.<sup>7</sup>

#### Box 4. Case study: MalariaGEN

MalariaGEN is a global research network with 24 units in 20 countries across Africa, Asia, Europe and North America. It is funded mainly by the Gates Foundation and the Wellcome Trust. The network brings together expert scientists to analyse human genetic variation in susceptibility to malaria.

The research is co-ordinated from Oxford University and was reviewed as a whole by the Oxford Tropical Research Ethics Committee. Each unit also applies for ethical clearance for particular projects from a local or national REC. MalariaGEN faces a number of ethical challenges, including: balancing standardisation with sensitivity to the diversity of cultures within and between countries; the implications of linking genetic data to ethnicity; collecting samples in difficult or emergency situations and developing appropriate methods to ensure valid consent and community participation.

The network has established an innovative system for dealing with such issues. An ethics team in Oxford supports the research units through site visits, ethics training, facilitating contact with local bioethics experts and setting up exchanges of experience and best practice. It has also designed a consent form template and produced guidelines on how this can be adapted to local contexts. Field researchers have found the team's support very useful. For more information see [www.malariagen.net](http://www.malariagen.net).

Since around 2000, efforts to improve research ethics in developing countries have been expanding. Several organisations fund training in ethical review for REC members, researchers and other stakeholders (see Box 5). Ethicists and researchers from the UK and developing countries believe international investment has improved the availability and quality of ethical review, particularly in Africa. Nevertheless, some are concerned that international programmes are imposing a Western system of ethical review on developing countries and that training at a broader level than RECs is needed, among institutional authorities and national officials.

#### Box 5. Research ethics training programmes

Initiatives to improve research ethics in developing countries:

- **The World Health Organisation's (WHO)** Strategic Initiative for Developing Capacity in Ethical Review supports capacity building based on both local values and international standards, including WHO's Operational Guidelines for Ethics Committees.
- **Fogarty International Center** (an international arm of the US National Institutes of Health) funds ethics courses in and for Africa, Asia and Latin America, aimed at professionals from these regions.
- **The Wellcome Trust** sponsors research, studentships, travel grants, seminars, pilot projects and other capacity building initiatives through its Ethics of Biomedical Research in Developing Countries grant schemes.
- **The Africa Malaria Network Trust's** Health Research Ethics Project, funded by the Bill and Melinda Gates Foundation, runs training workshops, an online forum and an 'Ask the Expert/Ethicist' programme.

### Ethical review capacity in the UK

Only three research institutions in the UK have RECs that specialise in reviewing proposals for research in developing countries: Oxford University, the London School of Hygiene and Tropical Medicine and the Liverpool School of Tropical Medicine. Some researchers believe RECs at other institutions may not have adequate knowledge or experience to assess what might be appropriate in the developing world. A REC dealing primarily with UK-based research, for example, may insist on an inappropriate informed consent procedure, or expect researchers from countries with sporadic internet access to apply for review online. Some UK RECs may be asked by external funders like the US National Institutes of Health to adjust their procedures and memberships, which could have time and cost implications.

### The informed consent process

#### Obtaining consent for research

A fundamental principle of research ethics is that a participant agreeing to take part in research should do so voluntarily and with sufficient knowledge and understanding of the procedures, risks and benefits involved. This is usually ensured through oral consultation and written consent. In clinical trials, the International Conference on Harmonisation Guideline for Good Clinical Practice is widely followed by both public and private sector researchers. This requires very detailed consent forms, which may not be feasible where potential participants have received no formal education. Determining what constitutes free and informed consent and the best method of obtaining it can be difficult in such circumstances. Explaining a genetic study or a randomised trial may be conceptually challenging, for example. Some projects use visual aids to give information in areas where literacy levels are low.

The International Conference on Harmonisation Guideline for Good Clinical Practice is followed widely by both public and private sector researchers in clinical trials. This requires very detailed consent forms, which may not always be feasible. Other forms of research needing special consideration of consent procedures include:

- those where participants might confuse a research intervention with healthcare;
- profit-making ventures, for which participants must be fully informed about potential commercial benefits;
- genetic studies (that might find variable susceptibility to malaria between ethnic groups, for example).

### Community engagement and consent

Engaging the local community in research planning and monitoring can help to ensure informed consent is obtained in a culturally appropriate manner, as well as address other concerns. Ethical guidelines suggest this can be done through local leaders, community advisory boards (CABs) or similar bodies, the appropriate route depending on the particular cultural context. A universal standard is that individual consent remains paramount, but this can be difficult to guarantee in hierarchical societies. Some ethicists and researchers note that, in practice, communities are often presented with a 'research package' pre-approved by RECs. Also, some scientists equate community engagement with gaining permissions from state authorities. Programmes such as those supported by DFID (Box 1) try to ensure local concerns and needs are addressed through employing researchers from host countries, liaising with local leaders and CABs and communicating in local dialects.

### Meeting local needs

RECs usually require a medical research proposal to demonstrate that a project will be relevant to local or national health needs. This is to ensure that research is not exploitative (a concern often levelled at private sector research in particular). Considerations include whether the research is likely to lead to interventions appropriate to the local context (heat-stable drug formulations, for example) and in a reasonable timeframe. Some ethicists and researchers have questioned the growing focus on genetic studies, predicting that these will have few concrete outputs in the medium term. They have also expressed concern that the focus of some funding streams on specific diseases may not correlate with the priorities of the communities affected.

### Individual and community benefits

Some benefits are integral to the research process:

- participants may be offered remuneration for travel costs or loss of earnings;
- diagnostic or treatment services may need to be enhanced to enable research to take place;
- researchers may learn new skills or be provided with improved facilities.

Sometimes projects offer benefits that bear little direct relation to a given research project. These can be offered on an individual or community basis: food for individuals or a grain mill for a community, for example. This is a sensitive area, as such benefits could be seen as 'undue inducements' to vulnerable people to participate in research,<sup>9</sup> thus projects have become nervous about offering them. Some researchers in developing countries see this as unfair, arguing that it would be unethical not to meet the basic needs of those taking part in research.

### Long-term benefits

RECs often scrutinise research proposals to see whether benefits will be sustained in the long term. Issues include:

- whether projects will build research capacity in-country rather than train local researchers overseas;
- what share participants should have in any profits resulting from intellectual property rights attached to the products of research;
- how any improvements in local healthcare provision will be maintained once a research project is over;
- whether participants should have preferential access to any new interventions and, if so, for how long.

Healthcare provision is generally seen as the duty of governments, although Oxfam argues that profit-seeking projects should guarantee participants treatment for as long as they need it. There is a concern that shifting this duty to companies or funders might dissuade them from investing in research, particularly for chronic diseases such as HIV/AIDS. The MRC, for example, cannot support healthcare provision in another country indefinitely. Projects can usually resolve these dilemmas by discussing post-trial arrangements fully with governments and communities before a project starts; it is when this does not happen that difficulties may ensue.

### Overview

- The UK funds biomedical research in developing countries from public and private sources.
- Research Ethics Committees in the UK and developing countries conduct ethical review of research proposals, but some may lack sufficient resources and expertise.
- How policies on informed consent, community engagement and benefit distribution are put into practice varies according to the contexts in which research projects are carried out.
- Funding for research may not match local priorities.
- Revisions to the Declaration of Helsinki in 2008 may have implications for UK policies on research ethics.

### Endnotes

- 1 World Health Organisation *Report on Infectious Diseases* (1999)
- 2 Chirac P and Torreele E, *The Lancet* (May 13 2006);367
- 3 Bhutta Z, *Bulletin of the World Health Organisation* 2002;80(2)
- 4 GlaxoSmithKline *GSK and Clinical Trials in the Developing World* (April 2006) www.gsk.com
- 5 Association of the British Pharmaceutical Industry *Global Health and the Pharmaceutical Industry* (July 2007)
- 6 Gevers S, *European Journal of Health Law* 2001;8(4)
- 7 Nuffield Council on Bioethics *The Ethics of Research Related to Healthcare in Developing Countries* (2002)
- 8 Kass N et al, *PloS Medicine* 2007;4(1)
- 9 Ezekiel EJ et al, *The Lancet* (July 23 2005); 366

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