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Ethics of healthcare research in developing countries

Medical and scientific research is now cross-national and cross-cultural. The relentless progress of globalization poses complex ethical questions for those wishing to do healthcare research in developing countries[1–4]. While some forms of research sponsorship are altruistic, much research is driven by economic or academic interests that may or may not reflect the needs of the host country. There is also the delicate matter of double standards. Does informed consent have the same meaning in a poor illiterate population as it does in, say, Basingstoke? What is an acceptable standard of clinical care in a resource-poor community? And there is the economic dilemma of whether and how to sustain an intervention, if the trial shows it to be effective, after the research is over. Perhaps most important of all is the issue of how to develop an ethical model for research and training partnerships between developed and developing countries—an approach with long-term advantage for the latter[5]. Happily, the era of 'safari research' is now gone, but the typical funding agency still pays scant attention to the audit of collaborative partnerships, especially with regard to development of the host country's research capacity.

A report from the Nuffield Council on Bioethics, *The Ethics of Research Related to Healthcare in Developing Countries*[6], is a timely contribution to the debate and a useful resource for governments, policy-makers and researchers. Its ethical framework is based on four sound principles of duty—the duty to alleviate suffering, to show respect for human beings, to be sensitive to cultural differences, and not to exploit the vulnerable. In the application of these principles, the social, cultural and economic context must be taken into account. The report recommends that:

- Countries should set national priorities related to provision of healthcare and to enhance their capacity to conduct research relevant to their needs
- When externally sponsored research is proposed which falls outside the national priorities, its relevance must be justified to the appropriate research ethics committees
- All countries should establish an effective system for the ethical review of research, which includes the establishment and maintenance of research ethics committees, independent of government and sponsors
- National and international sponsors of research should ensure that adequate provision is made for training in the ethics of research for professionals involved in research related to healthcare
- Development of local expertise in provision of healthcare research should be an integral component of any proposed research.

None of these ideas is drastically new. Among the most widely used existing international guidelines on research ethics are the Declaration of Helsinki, the Council for International Organisations of Medical Sciences Guidelines, and the Guidance on Good Clinical Practice. However, researchers do not always follow guidelines, and, if they do, their interpretations vary. Many developed countries have specific guidelines on research ethics, mainly tailored towards their own national research[4]. For example, guidelines in the USA are legally binding and American investigators are supposed to follow them no matter where the research is conducted. This poses a dilemma for American investigators working in developing countries since the regulations may not fit in with the host country's own regulations, standards of care, consent procedures and cultural expectations. Several developing countries, among them Uganda, Gambia, India, Nepal and Brazil, now have in place well established ethical review committees with experienced and well trained members. Others, such as Myanmar and Laos, have no functional ethics committees at all. Even where there is commitment to ethical review, meagre resources and poor infrastructure will make research projects hard to monitor. In the UK, the running costs of an ethics committee are about £36 000 a year and in the USA they can be as high as $500 000. Many developing countries lack regulatory mechanisms and a legal framework for biomedical research; moreover, poverty, poor pay and ignorance breed corrupt practices. The Nuffield report recommends international initiatives to establish research ethics committees, to train their members and to monitor their development. More controversially, it also declares that 'Funding should be provided for these purposes by those who sponsor research in developing countries'. The worry about this last recommendation is that ethics committee members might not be clearly impartial when assessing the pros and cons of a trial proposed by their sponsor.

What of informed consent? In general, the principle is that genuinely informed consent should be obtained from every participant in a study, perhaps sometimes preceded by the agreement of a senior member of the family or community member. So no news here either. The report has little to say on the matter of cluster-randomized trials, where communities rather than individuals are randomized to particular public health interventions. A dilemma that does attract close attention is the definition of a legitimate standard of care. This issue, when it arose in relation to clinical trials of antiretroviral agents in Africa, sharply divided the scientific community[7–9]. Angell, editorializing in the *New England Journal of Medicine*, declared that 'our ethical standards should not depend on where the research is performed' and that there is no justification for taking into account local economic conditions so as to provide 'a lower standard of care for some subjects than they would have received . . . in a different place'. But African researchers hotly dismissed this stance—which takes no account of local conditions and resource constraints—as imperialist[10]. The Nuffield report sides with the Africans, drawing upon the arguments of the philosopher Bernard Williams that what we mean by equality is not that people must always be treated identically, but that 'for every difference in the way men [*sic*] are treated, a reason should be given' that is relevant[11]. The working party recommends that the 'standards of care' provided to members of the control group in a research project should be developed in consultation with those who work within the country, and that the local ethics committee must be satisfied.

What does the working party say about the researcher's obligations if a controlled trial shows a treatment to be effective? Whatever happens, it declares, the decision must be made in principle before the research gets underway. Ideally, when the trial is completed, all participants who might benefit should be offered access to the intervention; and, if this is judged impossible, the ethics committee will need to be presented with strong reasons. This sounds fine in theory, but the reality is that the purpose of a trial is to test an unproven intervention, and a commitment to long-term provision of the intervention by the researchers, after the trial is over, is usually beyond the resources of the research team.

On the crucial questions of resources and capacity in developing countries, the working party can do little more than beg donors and funding agencies to take these recommendations forward. But the track record of these bodies offers little hope of stable funding for these activities. The progress made so far has come largely from developing countries—enlightened governments or academics. Perhaps the biggest disappointment of the report is the lack of specific advice on how to shift the balance from international (expatriate) to national agendas. Developing countries require institutions that are capable of high-quality research; it is on national rather than international staff that the sustainability of research findings and new interventions will depend. Although the report pleads eloquently 'we recommend that external sponsors of research should require that the development of expertise in research be an integral component of all research in developing countries', there are no detailed recommendations on the component of funding that should go to local infrastructure and how this might be monitored. None of the questions raised by this new report will come afresh to people conducting serious research in the developing world. For them, the important issues are resources, trained staff and infrastructure. On the special ethical issues raised by healthcare research, the ideal solution is for developing countries to take the lead and become self-sufficient. Programmes to advance this process would be a worthy object for outside funding.

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Animal experiments and the doctor

The debate on the use of animals in research tends to be polarized. At one extreme are the animal rights activists, implacably opposed to any use of animals, who cite cruelty, misguided experimentation and studies that offer nothing to scientific understanding or medical advance. These arguments are commonly targeted towards children and young adults—an influential and effective strategy. At the other extreme are scientists who proclaim how research in animals has led to important advances or cures for disease: 'would you refuse to treat your dying child with a drug that had been tested on animals?'. Yet the medical profession as a whole has remained rather quiet. The very group that relies upon animal experimentation for the treatment it provides, and is well placed to explain the potential benefits, is perceived as having discreetly distanced itself.

Both sides make good points. We must agree that not all animal studies have been conducted in an acceptable way and not all have been designed properly to answer a scientific or medical question. Conversely, it would be perverse to deny that certain curative treatments and diagnostic advances owe their emergence to animal experimentation. Despite the apparent gulf separating the groups, UK law enshrines certain principles to which both sides can agree, albeit with different emphasis and approach—replacement, reduction and refinement, the 'three Rs'. Put another way, if you don't have to use animals, don't; if you do have to use them, use the right number; and, if you design an experiment using animals, make sure that the maximum amount of useful data is collected for a minimum amount of suffering.

What are the prospects for replacement? According to a recent survey most establishments have a formal mechanism for discussing alternative approaches that avoid use of animals[1]. At a meeting at the British Association for the Advancement of Science very few in the audience answered yes to the conditional question, '*If* you could achieve the same advances without using animals would you continue to use animals in experiments?.' Unfortunately, in many instances realistic alternatives do not exist.

And reduction? Just as in clinical research, the issue of numbers and power calculations is sacrosanct. To use too many animals is unjustified, but to use too few—so that a result is uncertain or uninterpretable—is equally unacceptable.

As to refinement, procedures must be developed so that answers to questions can be obtained with the minimum of suffering. This is an area where many involved in animal experimentation are looking hard for answers.

Good practice sets higher ethical standards than the law. Institutions have established animal ethics committees to ensure that the three Rs have been appropriately addressed and that research on animals has been peer-reviewed with sufficient rigour to ensure that the experiments address an important question with a valid design. Most journals will encourage peer-reviewers to comment on the ethics of research on animals, and work that does not meet a high ethical standard is likely to be rejected. There remains much confusion about experimental approaches. 'Can't more be done in cells and using tissues'—yes, and it is being done, but it answers only certain types of question. 'Won't the sequencing of the human genome mean that animal experiments are unnecessary?'—no, because to find out what a gene does one often has to disrupt it and see how that alters the development or physiology of an animal. 'Isn't it likely that results in animals will be misleading'—the answer may be yes for certain aspects but an overwhelming no for defining general concepts or broad biological phenomena. 'Can't more be done in healthy volunteers and patients'—yes, but here too there are calls for more constraints, and one of those is better testing in animals before exposing human beings to risk. Whilst the results of chronic toxicological testing in animals can be hard to interpret, knowledge of the pharmacology of a new drug in animals will, and should for the forseeable future, remain a prerequisite to first administration in man.

Medical practitioners—not just clinical scientists but full-time clinicians as well—should join the debate about animal experimentation; they are in a good position to correct misunderstandings and place arguments in a clinically relevant context. To paraphrase a statement from the Royal Society: the medical profession should condemn activities that break the law in pursuit of a particular position, but be part of the attempt to maintain and strengthen an ethical approach to the use of animals in research through discussion and debate.

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Can patients with cystic fibrosis have a career in the health service?

Patients with cystic fibrosis (CF) grow up in contact with a wide variety of health professionals, so it is hardly surprising that some wish to have a career in the health service. In an attempt to answer the question posed by the title, this editorial looks at three issues—the infection risks to the CF healthcare worker; the infection risks to the CF healthcare worker's patients; and the challenges of a health service career for an individual who already has to cope with the considerable demands of a CF therapy regimen.

Infection risks to the CF healthcare worker

Patients and a healthcare environment pose a risk to all healthcare workers, but for workers with CF the risks may be greater. Box 1 lists the main organisms that are likely to be of concern. The fact is that cross-infection has become a nightmare for all patients with CF. At first the fear was just of colonization with *Burkholderia cepacia*[1–3], an organism that exists in several different forms, each with its own pathogenicity. However, it is now known that patients with CF can all too easily acquire *Pseudomonas aeruginosa* from other patients[4–6]. For the patient not already colonized, a matter of minutes in the company of a patient who is colonized may be sufficient for cross-infection to occur, and the worry is even greater in the case of multi-antibiotic resistant strains of the organism. *Staphylococcus aureus* has always been a threat to patients with CF, and the advent of methicillin-resistant strains has intensified efforts to prevent cross-infection. A commonplace strategy is to cohort patients, and many CF units now run separate 'Pseudomonas', 'Non-pseudomonas' and 'Cepacia' clinics. Although there is controversy about how far one should take measures to prevent cross-infection—objective data are scarce—many units make strenuous efforts to keep CF patients apart from each other: gone are the outings for patients with CF to Alton Towers, the day trips to Blackpool, the CF holiday camps. But keeping patients with CF apart at school can be extremely problematic, and keeping CF siblings apart is well-nigh impossible. Some units in North America have persuaded their patients to wear a mask whenever attending hospital; but, as with most other strategies in CF, there is no objective evidence in favour of this practice.

Against this background, a healthcare environment such as a hospital is a minefield for the healthcare worker with CF, who is likely to be at far greater risk of harm from cross-infection than a non-CF healthcare worker. Plainly some areas in the hospital or community environment are riskier than others. Probably the most hazardous environment of all is the CF unit—a miserable conclusion, because this is just the place where having a healthcare worker with CF could be of particular value. There is a dearth of published evidence in this whole area, and there are no data on the relative risks of, say, working in an intensive care unit, a burns unit, an infectious disease unit or a respiratory unit. Similarly there are no data on the value of measures to protect the CF healthcare worker, such as wearing masks, gowns or gloves.

Box 1 **Potential infection risks created by healthcare workers with cystic fibrosis (CF)**

Risk to CF healthcare worker	Risk to patients from CF healthcare worker
Pseudomonas aeruginosa	*P. aeruginosa*
Multi-resistant *Pseudomonas aeruginosa*	Multi-resistant *P. aeruginosa*
Staphylococcus aureus	*Staphylococcus aureus*
Methicillin-resistant *Staphylococcus aureus*	Methicillin-resistant *Staphylococcus aureus*
Burkholderia cepacia	*Burkholderia cepacia*
Klebsiella	Klebsiella
Tuberculosis	*Stenotrophomonas maltophilia*
Non-tuberculous mycobacteria	Aspergillus
Viral respiratory infections	*Haemophilus influenzae*
Varicella	
Bordetella pertussis	

Risks to patients from CF healthcare workers

The risk to patients will depend on the nature of the organisms colonizing the CF healthcare worker's respiratory tract. Box 1 lists some of the more likely pathogens. If the CF individual has no cough, produces no sputum, and has no pathogenic bacteria in the respiratory tract, then there is no increased risk to patients. Alas, few individuals with CF have a completely symptomless respiratory tract. The large majority pose a threat to a greater or lesser degree, and regrettably there is no objective way to measure the hazard they present. Some situations are self-evidently very high risk—for example, a CF patient expectorating *S. aureus* on a surgical ward, or a CF patient with *P. aeruginosa* on a burns unit—but in most circumstances any risk will be less obvious.

The challenges of a health service career

Many individuals with CF are highly motivated to work[7,8]. In one small study of 15 CF adolescents who were followed up, 10 were working in professional, semi-professional or clerical jobs, 3 were attending college and just 2 were unemployed because of CF[9]. Not surprisingly, the most powerful predictors of being able to work are low disease severity and high self-esteem[9].

A patient with CF who is considering a health service career—or any other career for that matter—needs information on the duration and requirements of training, as well as the demands of the career. These factors must be considered against the need to maintain a therapeutic regimen which may include daily exercise, twice daily or more physiotherapy, various medications, and possibly admission to hospital. A patient with CF considering a health service career must also give thought to the long term, and what will happen if and when his or her health deteriorates.

Conclusions

This editorial paints a rather bleak and negative picture. The other side of the coin is that some people with CF have had immensely successful health service careers, and a diagnosis of CF should not be seen as a complete barrier to such a career. The individual with CF who is contemplating a career in the health service needs to consider the issues of risk, and to discuss these with both a CF physician and a specialist in occupational health. For the reader who wishes to explore the subject in greater depth, it is one of several topics covered in this month's supplement to the *JRSM*, based on the latest Section of Paediatrics symposium on CF[10].

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