

The Sixth Global Forum on Bioethics in Research: Report of a Meeting, March 2005

Purism or pragmatism

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The Sixth Global Forum on Bioethics in Research* brought together delegates from more than 60 countries. While there was agreement on broad principles, there was less consensus on how they should be applied.

Ask two bioethicists for an opinion and you are guaranteed two distinct views. When this was suggested to two delegates at the recent Global Forum on Bioethics in Research*, one agreed completely while the other vehemently denied it.

A bit harsh, perhaps, but ethical discussions are notorious for not giving clear and simple answers. Nonetheless, Global Forum delegates from more than 60 countries, who travelled to Blantyre, Malawi, to discuss ‘what happens when the research is over’, managed both to engage in constructive discussion and to come to some kind of agreement on many key issues.

Research involving people in developing countries raises challenging issues, particularly when the researchers or sponsors of research are from the developed world. The biggest problems usually arise from the great disparity in access to medical care in developing world settings and rich countries. But different social norms, as well as health and political infrastructures, can also trap the unwary.

It was clear from the meeting that there is little disagreement about the general principles governing such research. Where it gets tricky is working out how these principles are applied in practice. As Dr Jimmy Whitworth (London, UK) put it, “The devil is in the detail”.

Good practice is documented in several sources, notably the Helsinki Declaration [1] and guidelines such as those produced by the Council for International Organizations of Medical Sciences [2]. However, the meeting was characterised by an undercurrent of tension – crudely put, between the ‘purists’ on the one hand and the ‘pragmatists’ on the other. And at the risk of oversimplifying a complex issue, this often pits the professional ethicists against the practising researchers.

Yet the tension can be used constructively, to stimulate dialogue that leads to more informed opinion on both sides, and influences what actually happens on the ground in what is still a relatively young and developing field. This will only work if all parties

are firmly committed to making progress. Or, as Professor Malcolm Molyneux (Blantyre, Malawi) responded to Jimmy Whitworth, “The deity is in the determination”.

Post-trial access

Take the issue of access to an intervention (a drug, say) after a trial. Everyone agrees that researchers have an obligation to a trial population, who have volunteered and are being exposed to risk. But what does that mean in practice? Some would say lifelong access to the drug. But who would bear the cost and who would organise provision? It would be a considerable burden on researchers if it were their responsibility, and is not something they have been trained to do. Many sponsors would argue that healthcare provision is not in their remit.

It also presupposes that the trial gives an unambiguous answer, whereas healthcare decisions are generally better based on meta-analyses of multiple studies. Moreover, decisions on healthcare provision should surely be made by local governments, which may have other priorities and wish to use scarce resources in other ways.

And what about members of the population who weren't in the study? Shouldn't they have access to the intervention too? But the population could be huge – perhaps a whole country. So these are difficult questions, particularly when chronic diseases (such as diabetes) are involved.

An alternative approach is to say that treatment should be provided for a certain period after the trial, say five or ten years. This is a pragmatic solution that researchers and sponsors might favour, but it also means that a life-saving treatment might eventually be taken away from people. And providing a treatment means providing the capacity to deliver and monitor it adequately, and to recognize its potential adverse effects or failing efficacy (eg induction of drug resistance in a pathogen).

The overarching principle is again clear: study populations should benefit from any treatment tested on them. As World Medical Association President-Elect Dr Kgosi Letlape (South Africa) emphasised, if that is unlikely to happen, the research should not be done; it is simply unethical. But if there is the potential to implement, whose responsibility should it be?

The purist versus pragmatist tension highlights a terrible dilemma. The purist is striving to protect the interests of a vulnerable and disenfranchised population. But, pragmatists suggest, in doing so they may create disincentives that impede research projects aiming at providing benefits to those communities.

Standards of care

Equally difficult issues arise when the standards of medical care offered to trial participants are considered. The medical services available in a study area are almost certain to be well below those seen in developed countries. If researchers work within the existing system then their subjects may suffer – or die – from preventable causes.

But if developed world standards are adopted, this can be seen, under certain circumstances, as an undue inducement to take part. And, again, what happens at the end

of the trial? Can a rich-world system really be sustained and who would pay for it? How would people outside the ‘privileged’ group respond?

A trial can, and should, in practice, deliver ‘collateral’ benefits which, with foresight, can be made sustainable. These benefits include training of local health workers, other forms of capacity building and enhanced infrastructure, such as the introduction of new equipment or technologies.

Consent

In one area at least, almost complete agreement is possible. Informed consent, from individuals, is absolutely essential in every case. In many developing countries, some decisions are often made at community level, so community assent is also often needed – but this should be in addition to, not instead of, individual informed consent.

There are difficulties of course. As Sassy Molyneux (Kilifi, Kenya) has pointed out [3], the concept of ‘research’ may be alien to a culture – a local language may not even have a word for it. Can consent then really be considered informed? And how far should one go to ensure consent is fully informed? Some consent forms are now extremely long and difficult for participants to understand and complete. Yet they may be required to make a decision in a short time, while most decisions of comparable importance are only made after extensive consultation and discussion.

Methodology

One of the most dynamic – and contentious – areas is study design. Researchers may have a valid research question (e.g. does a vaccine prevent disease?) but they need to think very hard about how a trial should be set up to provide an answer.

The randomised controlled trial has been set up as the ‘gold standard’, but many participants questioned its appropriateness in poor-country settings. The control arm may get no treatment (placebo), even though the intervention may be known to be effective in other settings. Observational studies were also felt by many to be of questionable morality in areas of high mortality. They can be useful in planning the study design, but they also mean that people may die of preventable causes while researchers collect data.

This is an evolving area, but well-thought-out trials can both test an intervention systematically and also deliver health gains. Professor Zulfiqar Bhutta (Karachi, Pakistan), for example, described a trial of a typhoid vaccine in a poor urban area of Karachi, in which the control arm was given a different vaccine (against hepatitis C virus) instead of a placebo. This principle has been increasingly applied in vaccine trials in recent years.

Consultation

One consistent theme at the conference was the need to consult widely within the local environment. So, in the example above, Professor Bhutta discussed the trial extensively with local community leaders, both to obtain their support but also to shape the study design. The choice of control vaccine, for example, was theirs. But do the local ‘leaders’

really represent the people? This is a question that researchers may not be in a position to answer.

More generally, if a piece of research is being carried out to benefit a local population, it should be planned in close consultation with local ministries of health or similar authorities. This can be aimed at ensuring that an intervention, if proven medically, stands a chance of actually being implemented. Implementation will depend on ministry of health priorities, existing healthcare infrastructures and national budgets. Hence it is also useful to factor in economic analysis, to demonstrate to policy makers the benefits gained from a particular investment in healthcare.

Similar attention should be given to post-trial access and standards of care. These should be agreed in advance with the appropriate authorities and community representatives. This is unlikely to be straightforward, and some researchers may quail at yet another administrative burden. But it can greatly enhance the likelihood that their research will have a practical impact locally.

These trends also chime with the operation of public–private partnerships, which are assuming ever-greater importance in global health. All sides are endeavouring to work collaboratively, with shared aims, to tackle the most important local health problems. Without this sense of teamwork, suggested Jimmy Whitworth, the chances of a successful outcome are significantly reduced.

Issues

Over two days' active discussion, many issues were debated, and several emerged as key topics for further consideration.

Governance: With ethical conduct such an important issue, the role of ethical review committees becomes increasingly important. But who 'reviews the reviewer' to ensure that ethics committees are carrying out their role satisfactorily? Professor Doug Wassenaar (Pietermaritzburg, South Africa) described a systematic approach being implemented in South Africa, based on the new Health Act [4], to nationally accredit all Research ethics Committees, requiring that committee members are trained and retrained when necessary. There may be a need for something similar in many other countries.

Communication: A less frequently considered obligation to participants is to provide feedback about the research. Researchers hurry to communicate with their peers, suggested Professor Wen Kilama (Dar Es Salaam, Tanzania), by publishing their findings in the Lancet or other high-profile journal, but rarely take the time to explain their findings to their study group in a way that is understandable to them (sending them copies of the Lancet paper is not enough).

'Research fatigue': Can a research community become 'over-researched'? As Professor Doug Wassenaar emphasised, there may be sound scientific reasons why the same group of people are repeatedly studied (e.g. large epidemiological studies where considerable work is put into developing a research infrastructure). Then again, added Professor

Athula Sumathipala (Sri Lanka), populations may be used simply because they are convenient for the researcher, as has happened in Sri Lanka.

Potentially, the continued use of a population could introduce scientific distortions, or people may simply grow tired of taking part – ‘research fatigue’ – especially if they do not see any benefits from participation. On the other hand, there is also a ‘justice’ angle: if participating in research provides some level of benefits, should these not be spread around different communities rather than always concentrated on the same group?

The possibility of over-research has not been given much attention, but it is likely to be an increasingly important issue. However, the meeting seemed to concur that there are already sufficient provisions within existing international ethics guidance to prevent exploitation, making the increasing use of the terms ‘research fatigue’ and ‘over-researched’ unnecessary.

The pharma legacy: If the Global Forum audience is typical, there is a deep mistrust of pharmaceutical companies and their activities in the developing world. They are seen to be acting in their own interests, using study populations for their own ends rather than with a view to improving the health or welfare locally. This mistrust can be seen to be driving very protective attitudes, to ensure that vulnerable populations are not exploited.

While this is again laudable, the danger once more is that hardline attitudes may deter more altruistically minded researchers, such as those supported by government or charitable foundations. They generally are concerned with local issues and are philanthropically motivated. It is also clear that many pharmaceutical companies devote considerable effort and funds to developing products that will principally serve the interests of the poor.

There is a sense in which the motivations of study populations have shifted from altruism to self-interest. Research is carried out with groups because it is impractical to work with an entire population, but it is the entire population that should, in theory, be the ultimate beneficiaries. When this sense is lost – for example, if the sponsors of research are seen to be the main beneficiaries – it is understandable that study populations may say ‘what’s in it for me?’. With medical progress often ultimately dependent on the clinical trial, this is a worrying trend.

A former pharmaceutical company employee, Dr Catherine Royce (Geneva, Switzerland), now at the Drugs for Neglected Diseases Initiative, suggested that constructive engagement with pharmaceutical companies was a fruitful approach to pursue. But the patenting and pricing policies of large pharmaceutical companies, and the history of their use of clinical trials in developing countries, have clearly created deep feelings of resentment.

Conclusions

Issues of this complexity are not going to be resolved in two and a half days. Yet participants from a variety of backgrounds, cultures and continents found much common ground – and a platform on which to discuss disagreements. In its sixth meeting, the

Global Forum has clearly matured into a venue in which delegates, in the majority from developing countries, feel comfortable airing views and have growing confidence about expressing opinions.

With the Wellcome Trust issuing its position statement during the meeting [5] and the Nuffield Council on Bioethics publishing its report of research in the developing world [6], ethical conduct has become a critical element of modern biomedical research. Research ethics is not an add-on that a researcher considers at the end but an integral part of the research planning process. The meeting may have been entitled ‘what happens when the research ends?’ but in reality the question is, ‘what should be done before the research begins?’

References

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*The Sixth Global Forum on Bioethics in Research: ‘What Happens When Research is Over? Post Trial Obligations of Researchers and Sponsors’, Blantyre, Malawi, 17–19 March 2005.