an environment where we all know that clinical research is not only important, but also necessary for progress in the health of people worldwide.

As we struggle with these issues, it is hoped that we are not seen to be presenting ourselves as judging what defines a ‘developing nation’. One does not have to go as far back as the US Public Health Service-sponsored Tuskegee study to see that, unfortunately, we are still coming to terms with our own breaches of the science/ethic debate. To learn from the recent gene transfer study in Philadelphia or the even more recent asthma study in Baltimore (both resulting in the death of a subject) or the lead environmental study also in Baltimore to know that the USA is in no position to point fingers.

It is important to know that the concept of OCP, the workings of the International Conference on Harmonisation (ICH) and our relatively newly formed Office of Human Research Protection (OHRP) are working to help ensure the safety of human subjects on all studies under the influence of the US regulatory bodies.1

Reference


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Clinical research paradox

The Sounding Board article by Shapiro and Meslin,1 essentially an attempt to distill the National Bioethics Advisory Commission (NBAC) Report on international research2, presents a paradox. On the one hand it restates some of the weaker aspects of the NBAC report; on the other, it actually goes beyond the often nebulous NBAC document to delineate research protections stronger than those contained in the report.

The NBAC report is, in a number of respects, weaker than the recently revised October 2000 Declaration of Helsinki (DOH),3 still the most influential research ethics document in the world. While the DOH requires that patients in the comparison groups in research of new therapies receive the ‘best current’ therapy, regardless of where the research is conducted, the NBAC has created a loophole likely to be exploited by researchers who wish to provide only those therapies that are locally available (the ‘standard-of-care argument’). According to NBAC Recommendation 2.2, ‘Any study that would not provide the control group with an established effective treatment should include a justification for using an alternative design.’ Ethics review committee members, already predisposed to accepting the self-serving reassurances and justifications of researchers who are usually their colleagues, are likely to afford these researchers wide leeway.

Interestingly, Shapiro and Meslin make it clear that, if not the NBAC, reject the standard-of-care argument when it applies to life-threatening conditions. The only justification for exceptions to the DOH, they write, would be situations ‘in which the only useful research design, from the host country’s perspective, required a less effective intervention in the control group, if the condition being studied was not life-threatening and if the trial received approval from an ethics review committee in the host country as well as one in the United States.’ (Emphasis added.) They then go on to discuss the notorious Surfaxin trial exposed by Public Citizen (which would have randomised some infants with often-fatal Respiratory Distress Syndrome to placebo instead of one of four US FDA-approved surfactants),4 concluding that: ‘In studies of this kind involving a disease that is lifethreatening and one for which an established, effective treatment is available, a placebo control is not permissible.’ Public Citizen certainly agrees with that.

We also agree with Shapiro and Meslin that the current version of the DOH is written too restrictively with respect to placebo use. Public Citizen has long supported the use of placebos in the treatment of minor or self-limited conditions, or those in which the placebo effect or regression to the mean are particularly strong, even if effective treatment exists (regardless of where the study is conducted). Such conditions would include mild headache, seasonal rhinitis or studies of antihypertensive drugs that last no more than a few weeks. We do, however, strongly object to the use of placebos in serious conditions (including some listed as candidates for placebo trials listed by Shapiro and Meslin) and the exploitation of poor people’s poverty to justify such use through the standard-of-care argument.

Elsewhere, unfortunately, Shapiro and Meslin stoop to the low standard established by the NBAC. NBAC Recommendation 4.2 would allow research to take place in a developing country even if there was no guarantee that any intervention proved effective during the trial would become available in the country of testing: ‘In cases in which investigators do not believe that successful interventions will become available to the host country population, they should explain to the relevant ethics review committee(s) why the research is nonetheless responsive to the health needs of the country and presents a reasonable risk/benefit ratio.’ This is simply inadequate to prevent the exploitation of developing world patients in studies in which the knowledge gained can be used to generate profits in lucrative western markets but no benefits are provided to local residents. Ethics review committees throughout the world are likely to interpret the phrase ‘responsive to the health needs of the country’ liberally, particularly when millions of dollars in research funding are at stake. Instead, a system whereby sponsors and local researchers agree on paper prior to the trial how the drug will be made available locally after the trial, if it proves to be effective, should be implemented.

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Another point not addressed by Shapiro and Meslin, but included in the NBAC report, merits special mention. The report clearly recommends that studies by US companies submitted to the FDA would require ethical reviews both in the USA and in the country in which the research is conducted, as opposed to the current situation where only foreign approval is required. Not requiring domestic ethical approval is one reason that the only evidence for independent ethics review of Pfizer’s controversial study of trovafloxacin for meningococcal meningitis appears to be a
backdated Nigerian review. But the NBAC once again has engineered a loophole: ‘However, if the human participants protection system of the host country or a particular host country institution has been determined by the US government to achieve all the substantive ethical protections outlined in Recommendation 1.1, then review by a host country ethics review committee alone is sufficient.’ Unfortunately, Recommendation 1.1 is extremely vague; we are therefore concerned that in the future the NBAC report will be used to permit research that is subject to US government regulations without ethical review by US ethical committees.

Ever since the debate surrounding the unethical perinatal HIV prevention trials, in which HIV-positive women were denied the known-effective drug AZT, which could have prevented transmission to their infants, the research industry (primarily the pharmaceutical industry, the FDA and the US National Institutes of Health) has set about manipulating the existing ethical codes so that their behaviour in those and future trials with similar designs could no longer be deemed unethical. In their first such effort, the research industry was foiled at the October 2000 DOH, particularly over the standard-of-care argument, which was included in an early DOH draft but then summarily rejected. The current draft revision of the Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects is the next battleground.

The CIOMS draft is nothing less than a bald-faced and dangerous attempt to reverse the gains in the protection of research participants accomplished by the October 2000 DOH. The apparent intent is to create a ‘war of the documents’, so that researchers will be able to select a study design acceptable to them and then have an array of different ethical codes from which to justify their behaviour (document shopping?). To an extent, this has already been accomplished through the International Conference on Harmonisation (ICH); its monograph on Choice of Control Group in Clinical Trials is also intended to bolster the inappropriate use of placebos and is actively hostile toward active-controlled trials. Public Citizen has issued a critique of a draft of that document.

If the first phase in the development of evidence-based medicine was the growing primacy of randomised-controlled trials, the second was the increasing relocation of research from the academy to private physicians’ offices. Such research is coordinated by contract research organisations (we prefer the more informative designation ‘human experimentation corporations’ [HECs]), but quality control in these studies may be questionable. We are now entering the third phase – the increasing internationalisation of research, facilitated by improvements in transport and communication and driven by pharmaceutical companies’ seemingly limitless pursuit of low regulatory hurdles and the ‘drug-naïve’ patient. A recent US Health and Human Services Inspector General report points out that the number of new foreign investigators in the FDA’s database grew from 988 in the 1990-1992 period to 5,380 in the 1996-1998 period.

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Nonetheless, FDA inspections of foreign research sites are rare and the agency does not inspect foreign ethics committees at all. We appear to have entered an era in which the potential for the exploitation of vulnerable patients is greater than ever, yet research is increasingly conducted in locales that are least susceptible to the protection of participants. In the absence of greatly improved ethical codes – and the regulatory apparatus to police them – we can expect a future in which research will increasingly be tainted by the latest international ethics scandal.

References