Meeting report

Clinical trials in developing countries: Discussions at the "9th International Symposium on Long Term Clinical Trials", London, UK, 19–20 June 2000

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Abstract

This symposium provided a useful forum for the discussion of issues relating to the design and conduct of clinical trials. There is a need for greater awareness of the complexity of modern day trials, in which a host of statistical, logistical, regulatory and ethical issues are involved. Issues discussed ranged from the effect of sample size on the outcome, and subgroup analysis, to defining and maintaining discrete endpoints. Some useful debate centred on the use of meta-analysis and the current limitations of combining information from different data sets. This brought up the subjects of trial registries and raw data repositories for all clinical trials. Progress and relevance of the Cochrane collaboration were reviewed. The economics of clinical trials was another important topic. Regulatory issues such as the role of data and safety monitoring boards (DSMB) and the guidelines in place for effective data monitoring and progress analysis were discussed. Representatives of government organisations and industry gave both European and American perspectives. This report however focuses specifically on the section devoted to the subject of clinical trials in developing countries.

Keywords: clinical trial, developing countries, ethics, publishing, symposium

Introduction

The symposium was organised by the Clinical Trials and Evaluation Unit, Royal Brompton and Harefield NHS Trust (UK), in collaboration with The National Heart and Lung Institute (UK) and The Maryland Medical Research Institute (USA), and was held at the Royal College of Physicians, London (UK). The theme was "Advanced issues in the design and conduct of randomised clinical trials". Approximately 250 delegates attended from around the world. It brought together key people involved at the practice end of clinical trials (co-ordinators, medical personnel, epidemiologists), scientists, members of regulatory bodies, industry representatives, publishers, statisticians and data analysers. The symposium was divided into eight sessions addressing a range of topical and challenging issues in clinical trials: economic evaluation; use of baseline data; innovative designs; the role of data and safety monitoring committees; sample size issues in clinical trials; meta-analysis as a guide to clinical practice; regulatory issues; and trials in developing countries.

The subject of clinical trials in developing countries was introduced briefly during the keynote address and covered in more detail in a session devoted to it. Two

speakers, Baruch Brody and Salim Yusuf, gave their views on ethical and organisational issues, using specific examples of trials carried out in developing countries. Richard Smith of the British Medical Journal addressed the subject of research and the publication of data from developing countries, highlighting the problems faced and outlining possible solutions.

Keynote address: "Clinical trials in the new millennium"

Professor David DeMets (University of Wisconsin-Madison, USA) outlined the role of the randomised clinical trial (RCT) in the advancement of medical technology and therapeutics, and how it has evolved over the 50 years since it was first introduced. Statistical methodology and information technology have been developed to improve collation, monitoring, analysis and access to the huge quantities of data involved in today's large international multi-centre trials.

The prospect for clinical trials has changed in recent years. In the USA, for example, government funding has been levelling out except in few key areas, such as breast cancer and AIDS research. The role of industry is increasing, often in partnership with academic institutions. Political and public interest in new clinical trials is also rising. Investors and many patient advocacy groups keenly monitor trial activity, and new policies on trial monitoring are being debated in the US Congress.

In this changing environment existing standards need to be re-evaluated in particular areas of medical technology such as medical devices, new procedures and alternative medicine, which DeMets felt were not properly regulated. He stressed that the development of revised standards should not result in high costs for industry, which have become a problem in the testing and approval of new drugs. DeMets also pointed out emerging areas likely to affect medical technology, such as the potential impact of genomics: if utilised constructively, results from genomics research could lead to the design of better, more accurate, treatment strategies and efficient trials.

The situation of developing nations contrasts with this vision of high-cost technological advancement in highly developed westernised countries. DeMets stressed the need to address the often complicated ethical, moral and logistical issues involving clinical trials in these countries.

Trials in developing countries: ethical issues

Dr Baruch Brody (Baylor College of Medicine, USA) explored the concept of medical imperialism in the conduct of trials in developing countries. He used as a direct example the criticisms raised of recent clinical trials for the prevention of vertical transmission of HIV in developing countries. The criticisms highlighted could be applied to clinical trials in general:

Injustice. Is it fair to deny a control group life saving therapy? The proposed revision of the Declaration of Helsinki states that the control group "should be assured that they will not be denied access to the best treatment otherwise available to him or her". However there is debate regarding the interpretation of this statement. Brody felt that the revision would be more plausible if it specified "….in light of the practical realities of health care resources available in that country". He felt this would force the focus onto issues of justice and less on what should be provided or actually is provided.

Coercion. If participants join a trial simply to receive treatment normally unavailable, and so not on a strictly voluntary basis, does this imply coercion? Brody dismissed this point, explaining that coercion generally implies a threat and simply offering someone a great opportunity should not be deemed unfair or coercive.

Exploitation. Is the treatment being tested unlikely ever to be available or of real use to participants? It is generally accepted that clinical trials should ideally be carried out in areas where the host community is likely to benefit from a positive outcome and where the treatment will be reasonably available. If not, and the results are likely to benefit only the richer developed countries carrying out the trial, the host population is being exploited. Should avoidance of exploitation be an ideal, or should it be a requirement prior to ethical approval? How stringent should the guidelines be? Who needs to be protected from exploitation - the trial participants only or the whole country in question? Brody pointed out that imposition of such long-term conditions might discourage drug companies from conducting such trials, because of the high cost of making the treatment available and accessible throughout the country. This may prevent important trials from being run. In his view, it is the individual participants in trials who are at highest risk of exploitation and it is their long-term welfare, which should be of primary importance.

Comment from the audience

One delegate felt there were arguments for not getting involved in trials in developing countries. Trialists, he said, should be extremely cautious before considering conducting trials in developing countries, pointing out some of the pitfalls involved: less than ideal data collection, false reporting by patients and theft of supplies. In reply, Brody pointed out that the critical public health issues plaguing many third world countries outweighed these considerations. He stated that it should be the moral imperative of richer developed nations to continue carrying out trials that benefit the participants in these countries, regardless of potential pitfalls.

Challenges of trials in developing countries

Dr Salim Yusuf (McMaster University, Canada) started his talk by giving an example from his personal experience

with the EMERAS/ECLA trials carried out in South America, which demonstrated advantages to carrying out clinical trials in developing countries. This project showed that simple well-organised trials paid off well above expectations. With the help of local staff it resulted in excellent quality data collection and follow-up. It was also the impetus for setting up "with minimum funding but maximum zeal and determination" other local projects and spin-off studies, data registries, local evidence-based clinical forums and resulted in an overall increase in clinical awareness.

He discussed the large successful high-quality trials carried out in developing countries such as India and China. Conditions there may be simpler and more suitable for certain trials than in other countries, yielding high-quality data. He noted that, although more time was often needed to set up these trials and to train staff, the "cleanliness" of data and the diligence of follow-up could be at least as good as that of equivalent trials in western countries. This was often due to the enthusiasm and motivation of local staff to address the very real problems existing in their communities.

Yusuf proposed several general issues for consideration when attempting to design international trials involving developing countries:

- Is the disease similar in different countries? (Epidemiological data are required to answer this question.)
- Is the trial relevant to the country: are the risk factors the same, is the treatment relevant and are the outcomes approximately the same?
- Do the culture and infrastructure exist to carry out this trial?

Determining the difference between "wants" and "needs", Yusuf felt, is crucial to providing effective health care solutions in a developing country. Western nations should be aiming to improve long-term healthcare in developing countries rather than providing 'quick-fix' short-term solutions. In particular, he mentioned the expansion of clinical research organisations (CROs) into developing countries. It is a damaging influence if they are there simply to carry out trials as cheaply as possible, in order to maximise profits, without real concern for the welfare of the local population.

He made it clear that organisers of trials in developing countries should aim to make the trials as simple as possible, and that it was crucial to understand local conditions: geography, infrastructure limitations, traditions, social organisation and politics, and to aim to work efficiently and sensitively within them. Long-term commitment to the project is essential, as is the understanding that more hands-on input would be needed than in developed countries, at all levels of the project. Researchers should be realistic and prepare for possibly extreme or adverse conditions. Trials in developing countries should not become a new form of neo-colonialism, however; researchers should see their role as helping, guiding and teaching, but not taking control.

In concluding this inspiring and passionate talk, Yusuf urged that trials in developing countries were possible and that the key was in the careful planning of large simple trials.

Publishing research in developing countries

Richard Smith (Chief Executive, *British Medical Journal*) addressed the disparities of publishing research from the developed compared to the developing world**.** He began with the statistic that, 20 years from now, 80–90% of all disability-adjusted life years lost would be in the developing world, as a result of the escalating levels of disease spread in areas such as Africa, India and in Southeast Asia. And yet by comparison only a minute fraction of relevant research may be carried out in these countries (he estimated less than 1%). What little research is done is often carried out on the diseases of the richer developing countries rather than the poor.

A *BMJ* editors' survey of 33 African research institutes brought to light what researchers there considered their biggest obstacles: poor institutional organisation, lack of funding, hopeless career structure, lack of mentors and support and very little research culture. In many African nations, research is often regarded as a luxury rather than a necessity – possible only when there is money to spare. Regarding publishing, barriers perceived were the use of English as the language of publication, lack of guidance in the preparation of papers, a fear of criticism by editors of journals in the developed world, and ignorance both of the way journals operate and of which would be suitable for publishing their research. They perceived a bias against research from their part of the world and felt that reviewers often did not understand the special difficulties of carrying out research in the developing world.

He predicted that, in 5 years, publication of most research (including clinical trials) would not take place in the paper form of journals, but on forums such as PubMed Central (http://pubmedcentral.nih.gov) or BioMed Central (http://biomedcentral.com). He felt sure some version of this form of publishing would "play out" in the long run.

Smith felt that, at present, most publishers were unfairly exploiting the system and actually devaluing it by breaking up research information. In the current system researchers do 99% of the work involved in trials, then edit and review manuscripts, and the copyright is then handed over to the journal. The academic community must then often pay high prices to access and archive this research information. He felt that this was less than ideal, "sucking out of

the system without giving anything back". In developing countries this high cost of subscription makes research information access even more difficult.

The World Wide Web has facilitated accessibility to data from different sources simply and cheaply. Sites such as PubMed Central and BioMed Central would potentially allow all research data to become easily available regardless of journal bias. An editor would not have to consider the journals' readership, issue lengths and other matters unrelated to the research itself. This is good news for research from the developed world, which sometimes is of interest only to readers in the originating region and which may not meet the needs of a general readership. The material would be freely available to everyone with Internet access – the availability of which is growing exponentially around the world.

Journals, he felt, could become more accessible to the developing world: by making Internet access free to users in poorer regions, and by having regional editions (where feasible). Smith also proposed that the standards applicable to research, and in particular to trials, in the developed world could differ for research generated in less developed countries. Such trials are being carried out under different conditions and their aims are likely to be different. He pointed out, for example, that research done in community medicine is evaluated differently from laboratory research. This does not have to imply lower standards - just different sets. Despite this proposal, Smith suggested that all trials published should conform to certain basic ethical guidelines and information should be fully disclosed.

Conclusion

This report has focused mainly on issues surrounding clinical trials in developing countries. Although this was only one of the many important issues raised at this symposium, it is nevertheless an important and complicated subject deserving attention and discussion. One point raised many times was the huge disparity in resources devoted to clinical trials in the developed world compared with those in the underdeveloped world, where the level of effective and realistic treatment for major population-threatening diseases lags far behind acceptable levels. Further discussion of these issues at future symposia should help to target trial resources more fairly towards areas of greatest need.

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