

SPECIAL ARTICLE

Trials in Developing Countries

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There is a real concern among international funding agencies and the pharmaceutical industry as to whether good clinical trials can be carried out in developing countries where resources and infrastructure are limited. The expertise may be there but the infrastructure may not exist to support good clinical trial practice (GCP). Nevertheless, through international collaboration it has been proved that clinical trials of GCP standards can be accomplished in Thailand. HIV-NAT (The HIV Netherlands Australia Thailand Research Collaboration) is one such example, comprised of the National AIDS Therapy Evaluation Centre (NATEC) in Amsterdam, the National Centre in HIV Epidemiology and Clinical Research (NCHECR) in Sydney and the Thai Red Cross AIDS Research Center in this tri-continent collaboration. The Center has successfully carried out 4 anti-retroviral studies in Thailand in less than 2 years.¹

The ethics of clinical trials in developing countries is a debate

SUMMARY Good clinical trials can be carried out in the developing countries but ethical issues concerning the trials are frequently brought up for international debate. The concern has its own merit but can be amended if investigators (local and international) pay serious attention to these criticisms and work out the way that will most benefit the trial participants. Although scientific progress is important, it must come after the rights, the safety and the benefit of the patients. Frequently, the ethical standard is delicately balanced, depending on who looks at it and from what angles they look. Critics, investigators, volunteers, sponsors and regulatory agencies have their own mandates, expectations and limitations, and thus they need to keep an open line of communication in order to benefit all parties involved.

issue frequently brought up in the international scientific arena. Critics are concerned that ethical standards may not be strictly observed by investigators in developing countries or if investigators from developed countries are involved, exploitation of subjects from developing countries may be a case. One such example is the recent ethical debate on the placebo-controlled trials in developing countries to reduce perinatal transmission of HIV.^{2,3} It is the purpose of this communication to bring up various problems of clinical trial design in developing countries from the perspective of an investigator

from a developing country. Examples to be given will deal mainly with trials in the prevention and treatment of AIDS.

Placebo-controlled trial

The aim of any clinical trial is to determine whether a new treatment is better than the existing treatment. Improvement may be in terms of efficacy, safety, convenience or cost. Therefore, it must always be compared with the stand-

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ard of care. If treatment does not exist or is unknown, placebo-controlled trial is the acceptable scientific approach like that of ACTG 076.⁴ ACTG (AIDS Clinical Trial Group) 076 was a placebo-controlled trial of zidovudine (ZDV) given to HIV-infected pregnant women from week 14 to week 34 of gestation through delivery and followed by another 6 weeks of ZDV to the newborns. This treatment regimen resulted in a two-third reduction in HIV vertical transmission, ie., from 25.5% in the placebo group down to 8.3% in the treatment group during an interim analysis.⁴ The efficacy of the treatment arm then resulted in premature termination of this placebo-controlled studies and ZDV has since become the standard of care in the industrialized countries. Once effective treatment or standard of care is established, then a placebo-controlled trial is no longer acceptable, particularly for treatments which can save lives, like ZDV in pregnant women. One may argue that placebo-controlled studies may still be justified in the country where the standard of care is no treatment. This may be correct if one has sound reasoning that the treatment that proved effective elsewhere may not be repeatable in another patient population. However, if this is to be done, placebo must be compared with the proved effective treatment, not the reduced treatment as in the 4-week ZDV placebo controlled study in Thailand.⁵ If the 4-week course of ZDV should turn out to be ineffective, nothing would be gained for the lives of newborns lost in the study. It would be more ethically acceptable if the trial design were full dose, reduced-dose compared to placebo ie. a 3-arm

study. If the reduced dose fails, at least one-third of the subjects in this 3-arm study would benefit from the trial. Nevertheless, investigators have to be prepared to stop a placebo-controlled trial promptly when the standard of care changes as resources become more available. An example of this is the premature discontinuation of a placebo-controlled trial of short course ZDV in pregnant women carried out by a university hospital in Bangkok when ZDV was made readily available by the Thai Red Cross donation campaign.³

Trial of a treatment which will never be affordable in the host country

Affordability is a relative term. How much to spend on healthcare depends on how much the country has and what else the country has to spend it on. It also depends on priority rating as judged by the vision and commitment of the politicians. Treatment which once used to be expensive can become cheap if demand increases, such as the case of vaccines used in the Expanded Program of Immunization (EPI). Therefore, we do not think that trial of an expensive treatment in developing countries would be unethical. It offers early access to treatment for some patients in need. It also gives clinical experience to the local experts who later will provide better care to the increasing number of patients who can afford the treatment. At the same time, the ongoing clinical trials will serve as a driving force for the responsible government officers to start doing something.

Treatment continuation after the completion of trial

This is a real ethical concern. Many patients agree for 24 or 48 weeks of treatment which, according to their views, is better than no treatment. Some patients use the resources saved during the trial period to extend the length of their treatment affordability after the end of the trial. Experienced investigators can sometimes negotiate for a longer period of trial or a longer supply of trial medications or can design roll-over studies. Examples are the antiretroviral trials being carried out by HIV-NAT in Thailand¹ In fact, some pharmaceutical companies such as Merck Sharp & Dohme have offered the life-long supply of their trial medications. This should set a new standard for companies sponsoring clinical trials.

Ethical conduct of the trials

It is certain that almost all trials in developing countries will have to receive ethical clearance before trials start. Patient information sheets and consent forms are the essential documents for ethical approval. However, how extensively the subjects are informed and how well the subjects from the developing countries who are in general, less well-educated, will understand the information given to them are in doubt. At times, the protocol is not strictly followed or even modified by the local investigators, while it is also ignored by the sponsor or the foreign coinvestigators. For example, many women who came early in their pregnancy were not informed about the full benefit of ACTG 076 but were persuaded to enroll in a short

course antiretroviral study which was supposed to be given to those who attended the antenatal clinic late in their pregnancy. Therefore, independent clinical monitors are important to ensure the ethical conduct of the trial. Another example of unethical conduct of clinical trials recently observed in Thailand was the discontinuation of antiretrovirals for patients enrolling into a phase II trial of a therapeutic vaccine although antiretrovirals were allowed in the protocol.

Ethical design of the trial

Nowadays, long-term single or double nucleoside trials are no longer attractive to patients in the Western world. On the contrary, such trials may still be welcome in the developing world where essentially nothing is available. However, investigators from the developing world must know how to negotiate for the best of their patients. Investigators in the developing world are in the best negotiating position with the pharmaceutical company since the company cannot do the trials elsewhere than in the developing countries. In addition, critics and ethicists around the world are watching for any unfair treatment that a rich country or company is showing to a poorer country. However, minimal

guidelines should be set to help less-experienced investigators from developing countries in negotiation. For example, if a new treatment is to be used singly, extensive close laboratory follow-up has to be instituted, such as CD4 and viral load measurements every 4-8 weeks. Safety and efficacy data must be closely reviewed by an independent data safety and monitoring board (DSMB). If treatment is effective, the company should provide lifelong supply of the medication to that patient. If treatment fails, the sponsor must be willing to provide the best available or the Western world standard of care to the subjects for a reasonable period of time.

Donor (sponsor) imperialism

Conduct of trials in developing countries may encounter conflicts between donor and recipient, since each party has its own expectation and esteem. Donors, particularly the collaborating foreign agencies may do the laboratory assays and the data analysis in their home countries instead of in the host countries. This in fact is understandable since work can be accomplished faster and with better quality this way. As a result, not all data are made available to the host institution. The same is also true for manuscript writing and

thus, the first authorship. Nevertheless, infrastructure development is one of the important issues in international collaboration. Laboratory strengthening and personnel training are essential for the developing countries and are the joint responsibility of the sponsor or the collaborating foreign agency. Therefore, budget allocation for infrastructure strengthening of the host institutions is one of the essential elements in the planning of clinical trials in developing countries.

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