Ethical considerations in clinical trials in Asia

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Abstract

Clinical trials are a kind of second choice by their very nature, involving uncertainty from the beginning. Such characteristics inherent in clinical trials necessitate ethical considerations. Ethical analysis emphasizes the importance in medical indications, patient preferences, quality of trials, and contextual features. Instances of clinical trial misconduct are usually due to insufficient analysis of medical indications, ignoring patient preferences, and the way in which investigators assess clinical trial results. Those problems are subjects of universal concerns. In the context of clinical trials, these are subjects inherent not only in Asia but also in every society, i.e., the “specific needs of each society.” Therefore, if there is any Asia-specific ethics, it is the issue of who will benefit from clinical trials or to consider the specific needs and benefits of Asian people.

Key words: ethics, clinical trial, Asia, placebo, culture

INTRODUCTION

Uncertainty is the prime reason why clinical trials are conducted. Uncertainty means that certain issues surrounding clinical trials have been left, which should be analyzed scientifically, morally and ethically. Medical morals dictate the particular actions and beliefs which regulate the day-to-day judgments of doctors, while medical ethics analyzes the universal principles on which the decisions are made (1). Engelhardt suggests that ethical or bioethical evaluation is required whenever unfamiliar moral issues are encountered (2). Therefore, ethical analysis is important in clinical trials which are now conducted internationally in countries with different values and morality. In dealing with such ethical issues, Jonsen's four-elements structure analysis is a convenient way to analyze the issues concerned (3). In this article, Jonsen's four-elements in ethical analysis, including "medical indications (beneficence or nonmaleficence)," "patient preferences (autonomy)," "quality of life," and "contextual features" are briefly discussed in relation to clinical trials. Some examples of analysis are presented, and whether there is any Asia-specific ethics in clinical trials is discussed.

ANALYSIS OF CLINICAL ETHICS

Medical Indications (Beneficence or Nonmaleficence)

The indications of medical intervention form the gateway for further diagnostic, therapeutic and preventive activities. Issues concerned at this stage may include medical goals, efficacy, risk and necessity, and overall goals. The patient has something to be cured or cared for. In preventive trials, healthy persons must have something preventable. Clinical trials are proposed because there are such obvious needs from medical indications. Medical indications are mostly technical, hence this element is not a serious concern in clinical trials. However, medical indications may become a subject of discussion, if any uncertainty remains in the setting up of clinical trials. For example, if the use of a surrogate endpoint is inevitable in the trial, it will definitely mean uncertainty in medical indications of that clinical trial. In an extreme situation, some medical goals are unrealistic today, but they may become realistic tomorrow. Thus, it is crucial to assess medical goals thoroughly before proceeding to

trials.

It should be emphasized that reviewing existing data on the test substance is an essential part of clinical trials, particularly for preventing adverse events and avoiding risks. This has been often neglected or oversimplified in the face of tempting medical goals. In some trials, certain risks are anticipated, but the trial can proceed with close interim analyses when benefits are likely to override risks. Since there is always uncertainty in the outcome, and certain risks are anticipated in trials, it is important to include patients' values in clinical trials. In practice, patients and/or the community should be involved throughout trials in assessment of medical goals and development of trial protocols (4,5). This leads to the second element of patient preferences.

Patient Preferences (Autonomy)

When medical indications are determined, investigators will proceed to the process of clinical trials. Issues concerned in this element are the ethical, legal and psychological significance of patient preferences, informed consent, patient competence, and refusal to participate. The protection of research subjects and quality control of trials have been articulated in such guidelines as the Declaration of Helsinki/World Medical Association, the Council for International Organizations of Medical Sciences International Ethical Guidelines for Biomedical Research Involving Human Subjects/World Health Organization and the Belmont Report/USA (6). Since the introduction of ICH-GCP (Good Clinical Practices developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use), this issue of patients' preferences has been solved at least theoretically (7). However, the claim that "informed consent was obtained" does not necessarily mean that the patient understood the information disclosed by the doctor (8), a common criticism of informed consent practice in the developing countries (9). Also, it should be acknowledged that the competence and judgment stability of the patient might wax and wane. In the context of the autonomy principle, special attention should be paid to vulnerable people and to other groups of subjects who are free in theory but oppressed by cultural circumstances.

In practice, there is always the possibility of breach of principles of informed consent, because medicine and doctors are by nature paternalistic. Investigators tend to withhold what they consider bad news from the patient or research subjects. Although such practices are an outgrowth of their good intentions, failure of information disclosure means that the principle of informed consent is violated. Some countries endorse the informed consent rule, even though it is not influential in modifying the clinical practice of doctors (10,11). Experience in these countries suggests that informed consent cannot be implemented by guideline alone, and legislation of the informed consent rule seems necessary. Thereafter, involvement of patients in assessment of medical goals is important to attain satisfaction in the outcome of the trial (12).

The issues of placebo relate to patients' preferences. Some people misunderstand and criticize the use of placebo in clinical trials, because they cannot differentiate placebo usage in trials and clinical medicine. In clinical trials, research subjects are informed they may receive either a test substance or a placebo. The subjects understand that there is no evidence as to which is better; there is no deception involved. This practice is ethical, although such a practice of giving unknown test substances to patients may violate the morality of some doctors. On the other hand, implication of placebo is different in clinical medicine. The patient is deceived, as if he or she were given an active drug in clinics. Such practices are sometimes ethically acceptable, when there are obvious reasons to permit the use of placebo. However, in most other cases such as giving patients with cancer pain a less effective drug to attain a placebo effect, placebo deception raises genuine moral and ethical questions, never to be allowed in clinics.

A problem may arise in clinical trials, when there is a certain expectation that a test substance may do a better job than a placebo. Indeed, the decision to participate in clinical trials may be influenced by "expectancy" of research subjects toward trials (13). However, the test substance may have adverse effects, and patients' and/or doctors' expectation does not necessarily mean it will work. For example, it is well known that antibiotics often resulted in worse outcomes than placebo in salmonellosis and other

infectious diseases (14). History of drug development and treatment modalities has shown countless failures with such drugs and therapeutic interventions despite high expectancy. Therefore, there is no doubt that a test substance must be examined in trial, even if the test substance is predicted to have high effectiveness. Placebo in such trials with high expectancy does not necessarily mean deception or breach of faith vis-à-vis the patients, so far as that information is disclosed to them. Yet the question may be still raised depending on the degree of "expectancy." In practice, this is a gray zone from the view of morality, i.e., one clinical trial may be ethically acceptable but morally wrong, when "expectancy" is high enough to predict the superiority of the test substance over the placebo. In the view of both investigators and patients, full disclosure of information is ethically necessary and close interim analyses are morally required in trials using substances with high expectancy. Since there is a gray zone involved, the decision to continue such trials is so difficult that one group may continue but another may stop the similar trial based on their interim analyses (15).

Quality of Life

The principal goal of medical intervention is to improve the quality of life (QOL) of the patient. Issues concerned in this element may include definition and evaluation of QOL, the agent and method to evaluate QOL, factors influencing QOL, and implications regarding sanctity of life. On this topic of clinical trials, the questions may include the appropriateness of endpoints, and assessment and interpretation of results. These additional issues are important because interpretation of these assessments is subjective, and hence open to biases.

In some trials, a surrogate endpoint is necessary for purely technical reasons. In other trials, investigators try to camouflage a surrogate endpoint as if a true endpoint. Moreover, a surrogate endpoint used in clinical trials is often misunderstood as a true endpoint by clinical doctors (16). Therefore, it is an ethical duty for investigators to objectively present their data as to what is obtained and what is left unknown by the trial. One such concern is an extensive use of relative efficacy rate or relative risk reduction (RRR) to describe the extent of efficacy of trials. RRR is a useful index

when an event rate is high in that disease. RRRs may be preferred by investigators because the resulting figures for RRRs are numerically larger (and seem more impressive) than for absolute risk reduction (ARR). To avoid bias and misunderstanding by both patients and doctors, ARR or NNT (number needed to treat, i.e. 1/ARR) should be presented along with relative efficacy rates for decision-making.

Other issues in assessment of results include the discrepancy between meta-analysis and megatrials (17), and the validity of stratified analysis of trials (18). Meta-analysis has been adopted widely to overcome the problem of trial sample size. However, the results of meta-analysis are influenced by several factors including publication and language biases, which may lead to false positive or negative results. The issue of stratification is important too. Overuse of subgroup analysis leads to improper emphasis on the results of subgroup analysis (18). Subgroup findings should be exploratory, and only exceptionally should they affect the conclusions of clinical trials (18).

Contextual Features

This element deals with broader social concerns surrounding clinical trials including the issues of the family and the third parties concerned; public notions including allegiance and advocacy, confidentiality, cost or public interest; policy, law and custom; religion, local and institutional circumstances where the trial is taken place. Since professional ethics is not exempt from general social ethics, it is influenced by the third parties concerned in clinical trials, when the claims of the third parties are ethically justified. A typical example is the recent disputes over clinical trials on prevention of tuberculosis and perinatal transmission of HIV in developing countries (6,19,20,21). Issues of for-profit multinational research subject recruiting activity, utility of resources (22), conflicts of interest between investigators and companies (23), and the role of media (24) are also relevant here.

Conducting clinical trials in developing countries raises different issues compared with the same trials in developed countries. Poverty, infectious diseases, poor nutrition, and low levels of health care systems not only affect the ease of performing trials but

also affect the medical indications (6). The issues of reproductive health and rights are totally different in developed and developing countries. Aid of medical resources alone cannot solve these problems (25). Complicated care systems of medical interventions cannot be adopted by countries with different cultures and traditions (6,21). Furthermore, susceptibility to test substances may depend on ethnicity. Therefore, questions already solved in one (developed) country sometimes need to be raised again in another (developing) country. This practice has been misunderstood not only by the general public but also by researchers, as if the latter trial were undermining the human rights of research subjects. On the other hand, it should be emphasized that clinical trials in developing countries to test drugs for use solely in developed countries violate the deepest principles of ethics (6).

The costs of medical care continue to rise in all countries. Even developed countries are struggling to constrain the costs of health care, although the problems of resource allocation may be greater among developing countries. Thus, cost-benefit analysis becomes a crucial issue not only in developing countries but also in developed countries (22). Treatment strategies must be formulated in the context of the health care system of each country, although a “double standard” should be avoided.

ETHICAL ANALYSIS OF CLINICAL TRIALS

Although some of these four elements of ethical analysis overlap, the problems and questions of trials can be well illustrated by this analysis. Here, let us illustrate each element by the example of some clinical trials and drug development policies.

Questions from the View of Medical Indications

Solivudine is a potent herpesvirus DNA metabolism inhibitor of a deoxyuridine-derivative. In September 3, 1993, it was released to clinicians with the catchphrase “a more potent and safer drug for herpes-zoster.” One patient died of bone marrow suppression on September 19, 1993, followed by a total of 7 seriously ill patients (3 dead) who had been given solivudine and anti-cancer fluorouracils. The Japanese Ministry of Health and Welfare (JMHW) circulated the Pharmaceuticals and

Medical Devices Safety Information (PMDSI) on October 12, 1993, but it could not stop patients with herpes-zoster from dying. By November 25, 1993, when solivudine was withdrawn from the market, a total of 23 were seriously ill, 15 of whom died.

Astonishing facts were disclosed later to mass media (26). Three patients had died of the same cause during the clinical trial, in a total of 244 enrollees. These three patients were enrolled at university hospitals, but these incidences were considered to be irrelevant to drug safety by university investigators. Furthermore, the company already had pre-trial toxicology results which showed the fatal adverse effects of solivudine on experimental animals. These animal experiments showed that the toxic effect was heightened when solivudine was given simultaneously with fluorouracils. These fatal results in animal toxicology experiments were hidden, and only the result of leucopenia was reported to the chief investigator and the JMHW. The Instructions for Doctors warned to use solivudine very carefully for patients who were being treated for other diseases. However, past experiences repeatedly showed that the Instructions for Doctors and the JMHW's PMDSI would not change the prescribing behavior of Japanese doctors. That was exactly what happened in this case.

In epilog, the staff of this drug company sold out their shares in the stock market, immediately before this case became exposed by mass media. The attending doctors and the drug company accused each other, each saying the other was responsible for this tragedy.

Questions from the View of Patients' Preferences

Since the introduction of ICH-GCP, there should be no question about this element, because strict adherence to the informed consent rule becomes necessary for clinical trials in every country. However, it is still a problem in trials involving cancer patients in Japan; many cancer patients are not told the truth. In other words, some hospitals endorse a strict informed consent rule, but others loosen the rule and exclude cancer patients. They continue to obtain consent from the family, isolating the patient from decision-making. The JMHW appears to accept this breach of the rule as part of a "Japanese form" of informed consent, based on paternalism and interpreted differently

from Western society (27).

Although concealing the truth from cancer patients was once a widespread practice, it has been shown that this practice does not have any clinical rationale (28). Even in Japan, truth disclosure is practiced without causing unpredictable problems in cancer patients (28). This issue is often attributed to cultural and ethical issues. However, it has been pointed out that in this issue of truth disclosure cross-cultural difference refers to the degree of understanding, whereas “culture” simply means the historically maintained current practice (29). Thus, exclusion of cancer patients from the informed consent rule is by no sense rationalized.

Questions from the View of Quality of Life

Drug policy is dependent on assessment and interpretation of data obtained from clinical trials and studies. Problems in this element are exemplified by the issue of non-steroidal anti-inflammatory drugs (NSAIDs) and Japanese influenza encephalitis/encephalopathy. It is well known that peculiar influenza encephalitis/encephalopathy is prevalent among infants exclusively in Japan (30,31). This is not a recently emerged phenomenon; the JMHW has set up several study groups to investigate this disorder. One of their aims is to elucidate the link between encephalopathy and NSAIDs, considering the relationship between Reye’s syndrome and aspirin. One JMHW study group found that encephalopathic infants who had been given NSAIDs had a significantly higher fatality rate than those who had not (32). The latest JMHW study group found adjusted risks of fatality among clinical encephalopathic infants (odds ratio, 95 % confidence interval) of 4.60 (1.03 to 20.49) and 3.05 (1.01 to 9.21) for mefenamic acid and diclofenac sodium, respectively (33). The result was confirmed with respect to diclofenac sodium in the following year (34). The JMHW drew the conclusion, alleging that the role of NSAIDs in encephalitis/encephalopathy were not clear yet (34).

Ironically, the high prevalence of encephalitis/encephalopathy (despite the absence of aspirin usage in acute febrile viral illness in Japan) is employed as evidence against the aspirin theory of Reye’s syndrome (31). However, the fact is that NSAIDs such as

mefenamic acid, diclofenac sodium, and others, are routinely prescribed for infant acute viral febrile illness by doctors in Japan. Often infants are given a combination of antipyretics and one or two NSAIDs, as shown in the results of the JMHW study groups (32,33). If aspirin relates to Reye's syndrome, the Japanese situation is likely to become even more serious than those countries where only aspirin was used for febrile children. These findings seem sufficient to recommend banning NSAIDs from infant acute viral febrile illness, at least until NSAIDs are found innocent in encephalopathy. Yet no such policy conclusions have been adopted; only the JMHW has advised doctors not to use diclofenac sodium for established influenza encephalitis/encephalopathy (34).

Questions from the View of Contextual Feature

The ethical issues include the rationale for conducting additional trials after positive results in another country, justification for inclusion of placebo groups, acceptance of "local standard of care," the quality of informed consent and other site-specific issues regarding medical intervention. Although these have been discussed extensively before (6,19,20,21), the value of "equivalency study" and use of placebo deserve further clarification.

Perinatal transmission of HIV occurs at a rate of 15 to 25 % in developed countries (with bottle feeding) and in 20 to 30 % in developing countries (with breast feeding) (35). Although zidovudine did not always prevent vertical transmission of HIV (36), some studies showed that vertical transmission was not observed in a total of 11 cases who had been given zidovudine during pregnancy (37,38). These highly promising data, though preliminary, had been available at the time of protocol development of the PACTG 076 study (39). Therefore, zidovudine was expected to prevent vertical transmission of HIV in the PACTG 076 study. The result of the PACTG 076 study showed that about 17 % benefited but 8 % were irrelevant to this very sophisticated method. If the PACTG 076 regimens had been introduced to the Thai trial (40) as an "active control arm," the expected absolute reduction rate would have been 17 %, a figure not very different from the corresponding figure (15 to 25 % minus 0/11 %) at the time of protocol development of the PACTG 076 regimen. If the first Thai study had

been unethical, the PACTG 076 study would have been also unethical. Thus, the use of placebo was an issue of medical indications rather than a contextual feature.

On the other hand, the issue of “equivalency study” belongs to this contextual feature; the question becomes: for whom the equivalency study was intended. There were three possible outcomes in the equivalency study between the PACTG 076 and the oral short course zidovudine (OSCZ) regimens for prevention of perinatal transmission of HIV, namely (1) the PACTG 076 regimen were superior to the OSCZ regimen, (2) the PACTG 076 regimen were inferior to the OSCZ regimen, and (3) the two regimens resulted in equivalent outcomes. In any of these three possible outcomes, the very sophisticated procedure of the PACTG 076 regimen would have never been implemented in developing countries, whereas the OSCZ regimen could have been introduced to developed countries if this regimen had been equal or superior to the PACTG 076 regimen. Thus, obviously the “equivalency study” was meant for developed countries. If the equivalency study between the PACTG 076 and the OSCZ regimens had been necessary, it should have been performed in the developed countries where both regimens were possible. It is true that about 20 (10 %) of the research subjects would have benefited from such an “equivalency study” in the Thai trial. Therefore, the “equivalency study” is not wrong in a moral sense. However, the inclusion of the effective regimen limited solely for comparison within the particular clinical trial, without intention to implement that effective regimen to people after the trial, would be ethically questionable.

Shorter course and/or smaller dosage regimens sometimes may be superior to lengthy authentic regimens (41). These regimens were tested primarily to benefit people in developing countries where target diseases were prevalent. Eventually, these less burdensome regimens have been found to be beneficial to people in developed countries as well. So the crucial question of the contextual feature is the matter of who benefits from clinical trials. One such issue was raised recently, regarding a trial of hepatitis E virus vaccine in Nepal (42). This trial is aimed to benefit people in developed countries as well as those living in developing countries. However, people in developing countries will benefit more by sanitation and development of health care

infrastructures than by vaccines (42). Furthermore, based on the global economic system (including health care resources), it is likely that people and pharmaceutical companies in developed countries will benefit more than people in the developing countries where vaccine trials are conducted. Assurance of continuous benefits is needed for the people in the country where such clinical trials are conducted.

IS ETHICAL ANALYSIS NECESSARY FOR CLINICAL TRIALS?

Whether one particular substance is called a drug or a toxin depends on humans' reaction. Clinical trials are conducted because there is ample prior assessment evidence or expectation that the test substance will be beneficial for humans. Unfortunately, this is not true in all cases, so this mode of action has to be studied first in trials before general implementation among clinicians. Therefore, clinical trials are a kind of second choice by their very nature, involving uncertainty from the very beginning. Such characteristics inherent in clinical trials necessitate ethical considerations for those concerned.

Problems in clinical trials have been presented with respect to the elements most relevant to ethical analysis. Medical indications are important in decisions to start clinical trials, but are too often neglected when the goals are too tempting. The solivudine case illustrates what will happen if investigators close their eyes to unfavorable events and pharmaceutical companies hide their data. Investigators' conclusions may be distorted from the data they found, as described in the NSAIDs/encephalopathy studies in Japan. To assure the effect of the ICH-GCP, full disclosure of information is essential in clinical trials.

The argument regarding trials in developing countries emphasizes that benefits from clinical trials should be shared by the people who contributed to the trials, not solely by the people who ordered them. Unfortunately, there are conflicts of interest between research subjects, investigators, and pharmaceutical companies. The pharmaceutical companies in developed countries who usually sponsor clinical trials will not benefit immediately from the improvement of health care infrastructure in developing countries. The situation may be getting worse, particularly for research

subjects and health care recipients among developing countries, from increasing competition and pressure from globalization of the economy, in which pharmaceutical companies are heavily involved. Then, the principle of sharing benefits with subjects should always be remembered in clinical trials.

Ethical consideration itself implies that there is moral argument. Moral argument among moral strangers is necessary to give society temperate tension and to keep advancing towards a healthier society. However, it is essential that discussion is based on full understanding of medical science and other ethical considerations implicated in clinical trials. At the same time, when morals and ethics are differentiated, there is always a hazard that ethics will be used by investigators and pharmaceutical companies as an excuse to avoid their moral duties to research subjects. Ethics should not be used as a waiver from the moral duty of the investigators in clinical trials.

IS THERE AN ASIA-SPECIFIC ETHICS IN CLINICAL TRIALS?

The problems in clinical trials described here are mostly derived from incidences in Japan. Japan has suffered from a number of erroneous JMHW decisions which resulted in countless victims of chloroquine retinopathy, thalidomide embryopathy, and HIV infection through blood products (26). This misconduct was mostly due to insufficient analysis of medical indications, ignoring patient preferences, and assessment of the results of clinical trials by investigators. These problems have been caused by sabotage by persons who should have had the responsibility to act properly. Therefore, these problems were not derived from Asia-specific values. Indeed, most issues in ethical considerations of clinical trials are subjects of universal concerns, as discussed extensively concerning the recent Gelsinger case at the University of Pennsylvania in the United States (43).

It has been said that the difference in morality is particularly marked between Eastern and Western values. Certainly, there is Asia-specific morality which constitutes a contextual feature of ethical analysis. Such Asia-specific morality is more important in clinical medicine than in clinical trials. On the other hand, there are social issues relating to Asia-specific contextual features of clinical trials. These are

subjects inherent not only in Asia but also in every society, the “specific needs of each society.” If there is any Asia-specific ethics, it is the issue of who will benefit from clinical trials. Globalization tends to ignore particular society’s needs, especially those of developing countries. When clinical trials are planned in Asia, it is the ethical duty of investigators and pharmaceutical companies to consider the specific needs and benefits of Asian people.

In conclusion, the ethical analysis described here is really synonymous with the basic principles of the Declaration of Helsinki regarding clinical research involving humans (44). It is also summarized in the three principles articulated in the Belmont Report, i.e., respect for persons (the recognition of the right of persons to exercise autonomy), beneficence (the minimization of risk incurred by research subjects and the maximization of benefits to them and to others), and justice (the principle that therapeutic investigations should not unduly involve persons from groups unlikely to benefit from subsequent applications of the research) (6).

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