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Proposal of Efficient Clinical Trials by using the Genomic Information

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Abstract

Under current clinical trials, a new drug could be authorized when a patient has no effect ("non-responder") on an existing drug. This leads to unnecessary adverse effect and high medication cost. Recently, it has become possible to change the patient's treatment depending on their genomic information, which is called "personalized medicine". It has a big benefit to patients by efficient treatment and lower cost, however, pharmaceutical companies hesitate to pursue personalized medicine, because of large development cost with very little market size, and not a matured methodology. In this paper, we will describe an efficient clinical trial, which will have a benefit to pharmaceutical companies by decreasing the cost for clinical trial, and early approval of the drug, with less adverse effect.

We will begin by describing a small size clinical trial, within a short period of study, using the patient's genomic information. We calculated the statistically required numbers of subjects and compared the cost for the current big clinical trials and the small clinical trials, excluding non-responder, by genomic information by simulation.

Keywords:

clinical trials, SNPs, personalized medicine, development cost

1. Introduction

Recently, the importance of "personalized medicine" is emphasized when a suitable treatment is selected according to the "constitution" of each patient. In the near future, it is expected that the drug and dose can be determined based on the genetic information including SNPs (single nucleotide polymorphisms) of each patient.

When personalized medicine becomes more available, unnecessary administration of drugs to non-responders can be avoided, and dose can be optimized. Also, medical expense in general can be reduced, and unexpected adverse effect can be avoided. These advantages are beneficial not only to the patients concerned, but also to the society as a whole.

However, the pharmaceutical companies are not actively engaged in the development of "personalized medicine" because they are afraid of lost revenue, and other drugs would not be prescribed to non-responders. Furthermore, the procedure for handling genetic information is not fully established yet.

The purpose of this study is to clarify the benefit and loss for the pharmaceutical companies when they adopt "personalized medicine", that is, when they take advantage of genetic information in their clinical trials. Particularly, the benefit for the pharmaceutical companies in terms of following two points will be analyzed. 1. Development cost of new drug and period of clinical trial can be reduced because a clinical trial needs less subjects, 2. The new drug can be placed on the market earlier because the development period can be shortened.

2. Methods

1) Principle of sample size estimation

Generally, the sample size of a clinical trial is calculated according to an equation as follows, for example.[1][2][3]

$$n = \frac{\left\{ Z_\alpha \sqrt{2\overline{P}(1-\overline{P})} + Z_\beta \sqrt{P_1(1-P_1) + P_2(1-P_2)} \right\}^2}{(P_1 - P_2)^2}$$

$$where \quad \overline{P} = \frac{P_1 + P_2}{2}$$

(In case of chi-square test for the difference in ratio between two groups)

N: Number of necessary samples

P_1: Response rate in investigational drug group

P_2: Response rate in control drug group

Z: Value calculated from significance level (generally 1.96 at 5%)

Z: Value calculated from power (generally 0.84 at 80%)

For example, when the response rate in the investigational drug group is estimated to be 70% and that in the control group is estimated to be 60%, the sample size of each group is n=356 according to above equation. Similarly, when the response rate in the investigational drug group is 90% and that in the control group is 60%, then n=32. That is, if there is a large difference in response rates, thus small sample size will be sufficient. The size is calculated based on significance level (typically =0.05) and power (typically =0.80) specified in the protocol, and estimated drug

response rate and difference between the groups. The calculation differs depending on the test method used.

3. Result

1) Enhancement of response rate using specific SNPs (Investigational drug group vs. control drug group)

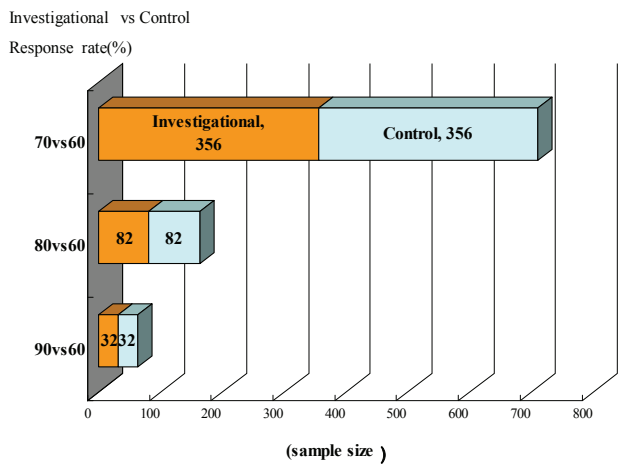

Figure 1 - Response rate and necessary sample size

By extracting and excluding non-responders based on SNPs information, the response rate of the investigational drug can be raised by 10%, e.g., from 70% to 80%. Then, the sample size of each group can be cut by 274 (356 to 82). In total, this means 548 cases will be unnecessary. This effect is more apparent when the response rate is low. Thus, this approach is highly useful in clinical trials in which only little difference in response rate is estimated between groups such as clinical trials of psychotropic drugs. In the approach above, additional cost may be necessary for a genetic testing before the clinical trial. Therefore, the total cost will be initially higher. However, if the sample size can be reduced by 548 in total, the cost as a whole will be less than the trial according to existing method. Furthermore, the cost of genetic testing is decreasing and the databases of genetic information are expanding day by day. In this circumstance, the genetic testing can be carried out at low cost in the near future.

2) Reduction of risk of adverse events

When any known adverse event (AEs) is anticipated due to causative gene, the patients concerned can be excluded from the investigational drug group. Thus, the risk of adverse events can be reduced.

Besides the safety enhanced by avoidance of an adverse event, the treatment for adverse event can be avoided. For the society in general, medical expense can be reduced, and for the pharmaceutical companies, compensation or indemnification cost can be avoided. In U.S, more than 2 million patients forced to be hospitalized because of the adverse effects in every year, hundred thousand people dies, and more than 70 billion health care cost wasted.

4. Conclusion

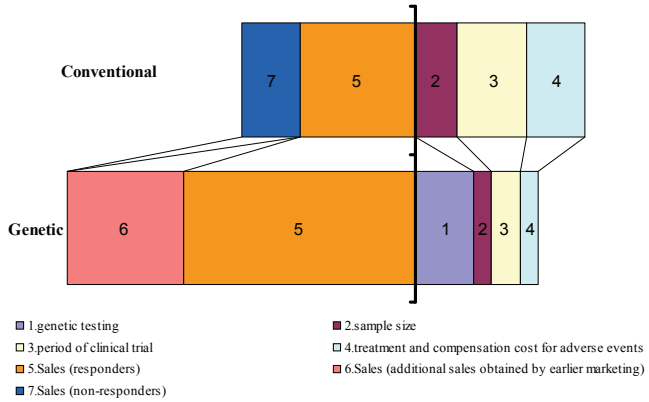

Figure 2 - Profit-cost structure in conventional clinical trial and clinical trial based on genetic information

Based on the discussion above, the profit-cost structure of a conventional clinical trial and a clinical trial based on genetic information can be estimated as Figure 2. According to our estimation, a clinical trial that takes advantage of genetic information is superior to a conventional clinical trial in terms of cost and profit. For example, the above shows, the development cost can be reduced by 5.5 million US dollar (10 thousand dollar /sample)[4]. Furthermore, the development period can be shortened by about 120 for 548 samples[4]. But, on the other hand, the sale for non-responders will be lost. However, because the drug can be marketed a120 days earlier than usual, the projected sales for the 120 days should be factored. In addition, risk of adverse events can be mitigated by screening patients based on genetic information such as SNPs. Reduction in compensation and indemnification cost, and reduction in medical expenses will be beneficial to the patients, the pharmaceutical companies, and the society as a whole. In a clinical trial using genetic information, temporary increase in process and cost may be inevitable. But, when genetic testing comes to be widely used, the cost will drop. Additionally, as the databases of genetic information are growing, it is apparent that the genetic testing will be simplified.

In view of the many benefits stated above, we expect the pharmaceutical companies to aggressively take advantage of genetic information in their clinical trials. We are now

planning profit simulation based on a clinical trial that was actually conducted.