Economic Advantage of Pharmacogenomics - Clinical Trials with Genetic Information

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Abstract. The purpose of this study is to clarify the benefit and loss for the pharmaceutical companies when they adopt introducing pharmacogenomics in their clinical trials (in the following description, clinical trials by using pharmacogenomics is called "pgx clinical trial"), that is, when they use genetic information in their clinical trials. Particularly, the benefit for the pharmaceutical companies in terms of following two points is 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. A survey conducted by Japan Pharmaceutical Manufacturers Association revealed that the pharmaceutical companies in Japan are interested in "pgx clinical trial". Specifically, 95% of the member companies (n=19) of the Association replied that the establishment of a guideline for pgx clinical trial by regulatory authorities are highly desirable. However, 65% of them (n=13) also replied that pgx clinical trial is difficult for the time being. It can be concluded that the pharmaceutical companies are positive about pgx clinical trial, but they cannot take a step towards it for several reasons: some of them may be worried their sales for non-responders will be reduced, poor understanding of pgx among the concerned parties, and not matured methodology of pgx clinical trial. This study shows that the advantage of pgx clinical trial outweighs its disadvantage. The sales may decrease because the drug is not used for non-responders, however, the number of subjects necessary for a clinical trial can be reduced, study period can be shortened and the drug can be marketed earlier. Furthermore, adverse events (AE) and adverse drug reactions (ADR) during the clinical trial and post-marketing phase can be markedly reduced. This represents a great benefit for the patients, pharmaceutical companies and the society as a whole.

Keywords. Biostatistics, Clinical trials, Mathematical models in medicine

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Introduction

In the current system for drug approval, a new drug is approved when the response rate of the drug is significantly higher than that of existing drug or placebo. In a clinical trial during development of a new drug, the drug is approved and allowed to be marketed if it can successfully show statistically significant effect compared to a placebo or a control drug (existing treatment). In the current method of a clinical trial, the drugs are compared between "groups" of subjects, that is, between a new drug group and a control group. The difference between responders and non-responders is often explained in terms of difference in subjects' profile. When the subjects have largely similar profiles, the difference is explained by a term called "constitution".

On the other hand, the importance of "personalized medicine" is emphasized where 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. According to the survey conducted by Japan Pharmaceutical Manufacturers Association in its member companies, 14 companies (70%) were afraid of reduced market size because the drug cannot be used for non-responders when genetic information is taken into account. 13 companies (65%) replied that pgx clinical trial is difficult because IRB (Institutional Review Board) does not approve pgx clinical trial (n=6, 30%), Ministry of Health, Labour and Welfare has not established a guideline yet (n=11, 55%), and pgx is not fully understood by patients and other relevant parties (n=17, 85%). However, given that 95% of the companies (n=19) replied that the establishment of a guideline for pgx clinical trial by regulatory authorities are highly desirable, the companies are not negative about pgx clinical trials itself [1]. It can be inferred that the pharmaceutical companies are interested in pgx clinical trial, but they cannot take action for several reasons: profit may decrease, pgx is not fully understood by concerned parties, and methodology of pgx is not mature.

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. Further purpose of this study is to appeal economic effect of the pgx to the pharmaceutical companies, and to advocate importance of the pgx and necessity of official guideline for pgx clinical trial to the regulatory authorities.

1. Examples of Personalized Medicine

For example, Herceptin is an anticancer drug by Roche used for prevention of postoperative recurrence or metastasis of advanced breast cancer. The drug is prescribed only for patients showing abnormal amplification of HER 2 gene (3+, highly positive), (2+, moderately positive). And after 90th, the study of the relations between drug metabolizing enzyme and drug metabolic rate has progressed. This study clearly shows the clear existence of Extensive Metabolizer (EM) and Poor Metabolizer (PM) which decided the differences of SNP of drug metabolizing enzyme. In case of
CYP2C29, PM rate is only 3% in white, but 20% in yellow race. If we can judge the
drug metabolic rate by using the differences of SNP’s information between the races, it
will lead the globalization of the clinical trials and be able to reduce the trials held in
each country. In this study, the design of clinical trial is examined in which the patients

<table>
<thead>
<tr>
<th>Items</th>
<th>Current</th>
<th>Personalized</th>
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<tbody>
<tr>
<td>Determination of usage and dose</td>
<td>Effect and ADR are determined based on the average.</td>
<td>Can be optimized for each patient according to the patient's capacity of drug metabolizing enzyme (e.g., CYP2C29, CYP2D6)</td>
</tr>
<tr>
<td>Determination of the number and profile of subjects to be enrolled</td>
<td>Determined using sample size estimation equation</td>
<td>Can be selected and response rate can be improved based on relevant genetic information</td>
</tr>
<tr>
<td>Medical expenses</td>
<td>Rises due to unnecessary administration to non-responders</td>
<td>Can be cut because unnecessary administration to non-responder can be avoided (pharmaceutical companies may lose their sales for non-responders)</td>
</tr>
<tr>
<td>Risk of Adverse Events</td>
<td>Unknown adverse event</td>
<td>Can be minimized based on information on causative gene and minimization of drug dose.</td>
</tr>
<tr>
<td>Cost of Clinical Trial</td>
<td>Usual recruiting cost</td>
<td>Temporarily increased because of the Genetic test</td>
</tr>
<tr>
<td>Difficulties of Recruiting the subject</td>
<td>Have to get consent from test subjects</td>
<td>Have to get the other consent for genomic information</td>
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are screened according to genetic information, and thus decreasing the total number of subjects. Table 1 shows comparison between current clinical trials and personalized clinical trials.

2. Methods

2.1. Principle of sample size estimation in conventional clinical trial

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

\[
n = \frac{Z_{\alpha}^2 \cdot 2(1-P) + Z_{\beta}^2 \cdot P_1(1-P_1) + P_2(1-P_2)}{(P_1 - P_2)^2} \quad \text{(where } \overline{P} = \frac{P_1 + P_2}{2})
\]

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

N: Number of necessary samples
P₁: Response rate in investigational drug group
P₂: Response rate in control drug group
Zα: Value calculated from significance level (typically 1.96 at 5%)
Zβ: Value calculated from power (typically 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 the 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 \( \alpha = 0.05 \)) and power (typically \( \beta = 0.80 \)) specified in the protocol, and estimated drug response rate and difference between the groups. The calculation differs depending on the test method used.

2.2. Principle of pgx clinical trial using genetic information

Figure 1 shows an example of 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. When the rate is raised from 80% to 90%, 82-32=50 cases can be reduced in both groups. This means the total of 100 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 a pgx clinical trial, additional cost is necessary for 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 and the study period as a whole will be less than the trial according to the existing method. Furthermore, the cost of genetic testing is decreasing and the banking and database of genetic information are expanding day by day.

![Figure 1. Response rate and necessary sample size (Control vs Investigational)](image)

2.3. 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.

Assume that a clinical test of a drug of which response rate is estimated to be 60% to 70% is planned for Japanese. When CYP2C19 is involved in the drug metabolism, 20% of the 712 subjects are estimated to be poor metabolizers (PM), so that the number of PM in the study group is 712 x 0.2=142. If ADR appears 10% of them, 14 subjects
will suffer from ADR, and if it appears 20% of them, 28 subjects will be affected. In a pgx clinical trial, PM can be screened out in advance, thus ADR can be avoided at the stage of clinical trial. If the screening cost is not covered by health insurance and the cost is 40 thousand yen (350 dollars) per a subject [3], the extra cost for screening is 40 thousand yen x 712 = 28.48 million yen (about 240 thousand dollars). However, should ADR occur, compensation about 120 million yen (1.1 million dollars) per a subject would be necessary in the case of death, and compensation about 490 million yen (4.3 million dollars) would be necessary in the case of permanent disability [4]. The extra cost of screening is not high compared to these expenses. When screening is conducted at Phase II (Ph2), ADR in Phase III and post marketing phase can be markedly reduced, which can compensate for the extra money used at the earlier stage. For the pharmaceutical companies, ADR can be avoided, thus, the compensation for the cost of hospitalization and treatment can be reduced. For the society as a whole, medical cost can be markedly saved. Cost of ADR is far from negligible. In the United States, more than 2 million patients have to be hospitalized due to ADR a year. 100 thousands deaths occur among them. The cost incurred by ADR exceeds 20 trillion yen, and 18 trillion yen of it is used for hospitalization (174.3 billion dollars). Medical cost for treatment of ADR amounts to 70 billion dollars a year [5].

3. Conclusion

As shown in Figure 2, the profit-cost structure of clinical trial is much improved in a pgx clinical trial compared to a conventional clinical trial. 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. In the above example, the development cost can be reduced directly by 1.6 million yen /subject x 548 subjects =87.7 billion at the clinical trial stage. Furthermore, the development period can be shortened due to less subjects. The days necessary for one subject are 3 to 4 days in average [6]. Thus, if median 3.5 days is used for calculation, 584/3.5= 157, that is, total 157 days can be reduced. The management cost and monitor dispatch fee during 157 days is hard to calculate, but these costs are reduced as well, further contributing to the reduction in the development cost [7].

On the other hand, the extra cost of screening and loss in profit due to smaller market can be calculated as follows. Cost of screening is 40 thousand yen x 712 subjects = 28.48 million yen (about 240 thousand dollars). Days necessary for the screening can be estimated to be 10 days. Thus, the days actually saved is 157 - 10=147 days. Besides, the entire sales for non-responders is lost, which represents a net loss. However, the drug can be placed on the market 147 days earlier than the conventional method because less subjects are used in a trial. Thus, the sale expected in these 147 days represents a net profit for the pharmaceutical company. Consequently, it can be concluded that the profit expected in the pgx clinical trial outweighs the extra cost and loss of the pgx clinical trial. Although Lipitor with the

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2 Excerpts from the material of “6th symposium of Kitasato University-Harvard School of Public Health” held on October 25, 2005. Mean cost per a sample in 29 clinical trials conducted in Japan by 17 member companies of Japan Pharmaceutical Manufacturers Association from April 2004 to March 2005. The cost includes fee for subjects, dispatch fee of monitors and management cost.

3 When the gene testing is contracted out to other company specialized in the test, 3 to 10 days are necessary for the test regardless of the sample size.
sales of about 1.5 trillion yen (13.7 billion U.S. dollars) is an exception, the sales of 18 drugs exceed 100 million yen (0.9 million dollars) a day [8]. Furthermore, the screening of relevant SNP can markedly reduce the AE and ADR during a clinical trial. This is a great benefit for the pharmaceutical companies given that the compensation for ADR is huge (hospitalization, death), and accompanying loss of credit is heavy for the company. What is more, the medical cost of the society as a whole can be saved as well. Thus, it can be concluded that pgx clinical trial is highly beneficial for the patient, company and the society.

For medical informatics, pgx clinical trials present a special challenge. Without appropriate security system for handling of genetic data, patients may be reluctant to participate in trials in fear of leakage of their data. Medical informatics may assume responsibility for establishment of security system crucial for pgx clinical trials.

Figure 2. Profit-cost structure in conventional clinical trial and clinical trial using genetic information

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. We expect the regulatory authorities to appreciate the advantage of pgx clinical trial, to establish well-defined guideline, and to conduct enlightenment activity for the people. Also, we expect the pharmaceutical companies to actively facilitate pgx clinical trials.

References