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Design and Analysis of Bridging Studies

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Preface

In recent years, the variations of pharmaceutical products in efficacy and safety among different geographic regions due to ethic factors have become a matter of great concern for sponsors as well as for regulatory authorities. However, the key issues lie on when and how to address the geographic variations of efficacy and safety for product development. To address this issue, a general framework has been provided by the International Conference Harmonisation (ICH) E5 in a document titled "Ethnic Factors in the Acceptability of Foreign Clinical Data" for evaluation of the impact of ethnic factors on the efficacy, safety, dosage, and dose regimen. The ICH E5 guideline provides regulatory strategies for minimizing duplication of clinical data and requirements for bridging evidence to extrapolate foreign clinical data to a new region. More specifically, the ICH E5 guideline suggests that a bridging study should be conducted in the new region to provide pharmacodynamic or clinical data on efficacy, safety, dosage, and dose regimen to allow extrapolation of the foreign clinical data to the population of the new region.

However, a bridging study may require significant development resources and also delay availability of the tested medical product to the needing patients in the new region. To accelerate the development process and shorten approval time, the design of multiregional trials incorporates subjects from many countries around the world under the same protocol. After showing the overall efficacy of a drug in all global regions, one can also simultaneously evaluate the possibility of applying the overall trial results to all regions and subsequently support drug registration in each of them. Recently, the trend for clinical development in Asian countries being undertaken simultaneously with clinical trials conducted in Europe and the United States has been rapidly rising.

With increasing globalization of the development of medicines, creating strategies on when and how to address the geographic variations of efficacy and safety for the product development is now inevitable. This book explicitly addresses the issues arising from bridging studies and multiregional clinical trials. For bridging studies, we will explore issues including ethnic sensitivity, necessity of bridging studies, types of bridging studies, and assessment of similarity between regions based on bridging evidence. For multiregional clinical trials, we dig into issues such as consideration of regional difference, assessment of the consistency of treatment effect across regions, and sample size determination for each region. Although several statistical procedures have been proposed for designing bridging studies and multiregional clinical trials, the statistical work is still in the preliminary stages. This book provides a comprehensive and unified summary of the growing literature and

research activities on regulatory requirements, scientific and practical issues, and statistical methodology on designing and evaluating bridging studies and multiregional clinical trials. Most importantly, we sincerely hope that this book can inspire in academia new research activities in the design and analysis of bridging studies and multiregional clinical trials.

Contributors

Herng-Der Chern
Center for Drug Evaluation
Taipei, Taiwan

Shein-Chung Chow
Duke University School of Medicine
Duke University
Durham, North Carolina

Christy Chuang-Stein
Statistical Research and Consulting Center
Pfizer, Inc.
Kalamazoo, Michigan

Chin-Fu Hsiao
Institute of Population Health Sciences
National Health Research Institutes
Miaoli County, Taiwan

Eric Tsung-Cheng Hsieh
Buddhist Tzu-Chi University and Hospital
Hualien, Taiwan

Hsien-Ming James Hung
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Silver Spring, Maryland

Yoichi Ii
Clinical Statistics
Pfizer Japan Inc.
Tokyo, Japan

Mari Ikuta
GlaxoSmithKline
Tokyo, Japan

Norisuke Kawai
Clinical Statistics
Pfizer Japan Inc.
Tokyo, Japan

Osamu Komiyama
Clinical Statistics
Pfizer Japan Inc.
Tokyo, Japan

Kazuhiko Kuribayashi
Clinical Statistics
Pfizer Japan Inc.
Tokyo, Japan

Kuang-Kuo Gordon Lan
Janssen Pharmaceutical Companies of Johnson & Johnson
Raritan, New Jersey

Yeong-Liang Lin
Center for Drug Evaluation
Taipei, Taiwan

Jen-pei Liu
Department of Agronomy
National Taiwan University
Taipei, Taiwan

Ying Lu
Beijing University of Technology
Beijing, China

Hiromu Nakajima
GlaxoSmithKline
Tokyo, Japan

Robert O'Neill
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Silver Spring, Maryland

José Pinheiro
Janssen Pharmaceutical Companies of Johnson & Johnson
Raritan, New Jersey

Hui Quan
Department of Biostatistics and Programming
Sanofi
Bridgewater, New Jersey

Weichung J. Shih
Department of Biostatistics
University of Medicine and Dentistry of New Jersey–School of Public Health
Piscataway, New Jersey

Kihito Takahashi
GlaxoSmithKline
and
Japanese Association of Pharmaceutical Medicine
and
Japanese Center of Pharmaceutical Medicine
Tokyo, Japan

Yi Tsong
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Silver Spring, Maryland

Hsiao-Hui Tsou
National Health Research Institutes
Miaoli County, Taiwan

Mey Wang
Center for Drug Evaluation
Taipei, Taiwan

Sue-Jane Wang
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Silver Spring, Maryland

Yuh-Jenn Wu
Chung Yuan Christian University
Chung Li City, Taiwan

Lan-Yan Yang
National Cheng Kung University
Taiwan City, Taiwan

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Bridging Diversity: Extrapolating Foreign Data to a New Region

Shein-Chung Chow
Duke University

Chin-Fu Hsiao
National Health Research Institutes

1.1 Introduction

In recent years, the possible influence of ethnic factors on clinical outcomes for evaluating the efficacy and safety of study medications under investigation has attracted much attention from both the pharmaceutical/biotechnology industry and regulatory agencies such as the U.S. Food and Drug Administration (FDA), especially when the sponsor is interested in bringing an approved drug product from the original region, such as the United States or the European Union, to a new region such as the Asia-Pacific region. As indicated in Caraco (2004), genetic determinants may mediate variability among persons in the response to a drug, which implies that patient response to therapeutics may vary from one racial/ethnic group to another. Some ethnic groups may exhibit clinically significant side effects, whereas others may have no therapeutic responses. Other ethnic factors that can distinguish new and original regions may include the social and cultural aspects of a region such as medical practice (e.g., diagnostic criteria), epidemiological difference (e.g., diet, tobacco or alcohol use, exposure to pollution and sunshine), and compliance with prescribed medications. As a result, the dose and dose regimen approved in the original region may not be appropriate (for achieving the desired therapeutic effect) for patients in a new region. Thus, it is important to demonstrate that the approved treatment at the original region will achieve *similar* or *equivalent* therapeutic effects (in terms of efficacy and safety) when applied to patients in the new region before it can be approved and used there. However, it should be noted that if there is evidence of therapeutic differences due to race or ethnicity, the dose and dose regimen of the

test treatment is necessarily modified to achieve similar therapeutic effect as observed in the original region.

In practice, the sponsor can conduct studies in a new region with similar dose and dose regimens and sample sizes to confirm clinical efficacy and safety observed in the original region for regulatory approval at the new region. However, duplicating clinical evaluation in the new region will not only require (and waste) already limited resources but also delay the availability of the approved treatment at the original region to patients in the new region. To overcome this dilemma, in 1998, the International Conference on Harmonization (ICH) issued a guideline titled "Ethnic Factors in the Acceptability of Foreign Clinical Data" (known as ICH E5) to determine if clinical data generated from the original region are acceptable in a new region. The purpose of this guideline is not only to permit adequate evaluation of the influence of ethnic factors but also to minimize duplication of clinical studies and consequently not to delay the availability of the approved test treatment to patients in the new region. This guideline is usually referred to as the ICH E5 guideline.

Following the 1998 ICH E5 guideline, regulatory authorities in different regions (e.g., Japan, South Korea, and Taiwan in the Asia-Pacific region) have developed similar but different regulatory requirements for bridging studies, which have led to different bridging strategies in different regions. These bridging strategies also raise some practical issues such as criteria for assessment of similarity in therapeutic effect between regions, sample size calculation and allocation, and statistical methods for data analysis and interpretation in bridging or multiregion studies.

In the next section, the possible influence of racial and ethnic differences on clinical outcomes is discussed. This justifies the need to conduct bridging studies when a sponsor is seeking regulatory approval in a new region. Section 1.3 provides a brief summary of ICH guideline and regulatory guidelines from the Asia-Pacific region (e.g., South Korea and Japan). Some current issues and bridging strategies are discussed in Section 1.4. Two successful examples for bridging evaluations are given in Section 1.5. Some concluding remarks are given in Section 1.6, followed in Section 1.7 by the aim and scope of the book.

1.2 Impact of Ethnic Differences

Since the completion of the Human Genome Project, there has been increasing evidence that genetic determinants may mediate variability among persons in the response to a drug, which implies that patient response to therapeutics may vary from one racial or ethnic group to another. As an example, Caraco (2004) pointed out that some diversity in the rate of responses can be ascribed

to differences in the rate of drug metabolism, particularly by the cytochrome P-450 superfamily of enzymes. While 10 isoforms of cytochrome P-450 are responsible for the oxidative metabolism of most drugs, the effect of genetic polymorphisms on catalytic activity is most prominent for three isoforms—CYP2C9, CYP2C19, and CYP2D6. Among these three, CYP2D6 has been most extensively studied and is involved in the metabolism of about 100 drugs including beta-blockers and anti-arrhythmic, antidepressant, neuroleptic, and opioid agents. Several studies revealed that some patients are classified as having "poor metabolism" of certain drugs due to lack of CYP2D6 activity. On the other hand, patients having some enzyme activity are classified into three subgroups: (1) those with *normal* activity (or extensive metabolism), (2) those with reduced activity (intermediate metabolism), and (3) those with markedly enhanced activity (ultrarapid metabolism). Dosages for most drugs are commonly determined by their pharmacokinetic behavior in a group of healthy patients, most of whom have extensive metabolism of CYP2D6 substrates. It is clear that for the CYP2D6-inactivated drugs, the "average doses" are too much for people with poor metabolism and too little for those with ultrarapid metabolism. It should be noted that the distribution of CYP2D6 phenotypes varies with race. For instance, the frequency of the phenotype associated with poor metabolism is 5% to 10% in the Caucasian population but only 1% in the Chinese and Japanese populations (Caraco, 2004). In other words, Caucasians are more likely than Asians to have abnormally low levels of CYP2D6, which metabolizes drugs such as antidepressants, antipsychotics, and beta-blockers.

Another example regarding the impact of ethnic factors on the responses to therapeutics is the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor gefitinib (Iressa). Recently, Iressa was approved in Japan and the United States for the treatment of non-small cell lung cancer (NSCLC). The EGFR is a promising target anticancer therapy because it is more abundantly expressed in lung carcinoma tissue than in adjacent normal lung tissue. However, clinical trials have revealed significant variability in the response to gefitinib with higher responses observed in Japanese patients than in a predominantly European-derived population (27.5% vs. 10.4%, in a multi-institutional phase II trial; Fukuoka et al., 2003). Paez et al. (2004) also show that somatic mutations of the EGFR were found in 15 of 58 unselected tumors from Japan and 1 of 61 from the United States. Treatment with Iressa causes tumor regression in some patients with NSCLC, more frequently in Japan. Finally, the striking differences in the frequency of EGFR mutation and response to Iressa between Japanese and American patients raise general questions regarding variations in the molecular pathogenesis of cancer in different ethnic, cultural, and geographic groups.

Recently, geotherapeutics has attracted much attention from sponsors as well as regulatory authorities. However, the key issues lie in when and how to address the geographic variations of efficacy and safety for the product development. It will strongly depend on the size of the market, development

cost, and the factors influencing the clinical outcomes for evaluation of efficacy and safety. If the size of the market for some new geographic region is sufficiently large, then it is understandable that the sponsor may be willing to repeat the whole clinical development program after the test product has completed its development plan and maybe obtain the market approval in the original region.

1.3 Regulatory Guidelines

1.3.1 ICH E5 Guideline on Bridging Studies

The ICH E5 guideline suggests that the new region's regulatory authority assess the ability to extrapolate foreign data based on the bridging data package by gathering information including pharmacokinetic (PK) data and any preliminary pharmacodynamic (PD) and dose-response data from the complete clinical data package (CCDP) that is relevant to the population of the new region and by conducting a bridging study to extrapolate the foreign efficacy data or safety data to the new region. In addition, the ICH E5 guideline also points out that evaluation of the ability of extrapolation of the foreign clinical data relies on the similarity of dose response, efficacy, and safety between the new and original regions either with or without dose adjustment.

By the ICH E5 guideline, the ethnic factors are classified into two categories. *Intrinsic ethnic factors* define and identify the population in the new region and may influence the ability to extrapolate clinical data between regions. They are more genetic and physiologic in nature (e.g., genetic polymorphism, age, gender). *Extrinsic ethnic factors* are associated with the environment and culture and are more social and cultural in nature (e.g., medical practice, diet, practices in clinical trials, conduct).

The ICH E5 guideline indicates that bridging studies may not be necessary if the study medicines are insensitive to ethnic factors. For medicines characterized as insensitive to ethnic factors, the type of bridging studies (if needed) will depend on experience with the drug class and on the likelihood that extrinsic ethnic factors could affect the medicine's safety, efficacy, and dose response. On the other hand, for medicines that are ethnically sensitive, a bridging study is usually needed since the populations in the two regions are different. The ICH E5 guideline has also listed critical properties of a compound that make it more likely to be sensitive to ethnic factors. These critical properties include nonlinear PK, a steep PD curve for both efficacy and safety, a narrow therapeutic dose range, high metabolizing rate, extent of bioavailability, potential for protein binding, potential for interactions, genetic polymorphism, intersubject variability, systemic mode of action, and

potential for inappropriate use. However, the ICH E5 guideline also points out that no one property of the medicine is predictive of the compound's relative sensitivity to ethnic factors.

The ICH E5 guideline also provides a summary of the types of bridging studies required in the new region. A bridging study could be a PK–PD study or a controlled clinical trial depending on the ethnic sensitivity of the study medicine, clinical experience of the drug class, extrinsic ethnic factors, and ethnic differences between the new and original regions. For example, if the regions are ethnically dissimilar and the medicine is ethnically sensitive but extrinsic factors such as medical practice, design, and conduct of clinical trials are generally similar and the drug class is a familiar one in the new region, a PK–PD study in the new region could provide assurance that the efficacy, safety, dose, and dose regimen data derived from the original region are applicable to the new region. On the other hand, if there are doubts about the choice of dose, there is little or no experience with acceptance of controlled clinical trials carried out in the foreign region, medical practices (e.g., use of concomitant medications and design or conduct of clinical trials) are different, or the drug class is not a familiar one in the new region, a controlled clinical trial will usually need to be carried out in the new region.

Although the ICH E5 guideline has provided a general framework for evaluation of the impact of ethnic factors, many questions still remain. First, the ICH E5 guideline did not provide precise and definitive criteria for assessment of the sensitivity to ethnic factors for determining whether a bridging study is needed. Consequently, both regulatory authority in the new region and the sponsor will not have criteria and a method for an objective and impartial evaluation of ethnic sensitivity and necessity of a bridging study. Under the circumstances, any proposed approach for the assessment of the necessity of bridging studies could be subjective and controversial and may not be accepted by the regulatory authority and sponsors in the new region. Second, when a bridging study is conducted, the ICH E5 guideline indicates that the study is readily interpreted as capable of bridging the foreign data if it shows that dose response, safety, and efficacy in the new region are similar to those in the original region. However, the ICH E5 guideline does not clearly define the similarity. For assessment of similarity, a number of different statistical procedures have been proposed based on different definitions or concepts of similarity—for example, batch similarity in stability analysis for shelf-life estimation, similarity in drug release for comparison of dissolution profiles between drug products, similarity in drug absorption for assessment of bioequivalence between drug products, and the concept of consistency between clinical results. While those statistical procedures may be useful, well-defined, and scientifically justifiable, criteria for assessment of similarity based on bridging evidence need to be addressed in the future.

Note that following the ICH E5 guideline, many countries in the Asia-Pacific region including Japan, South Korea, and Taiwan not only have developed similar but slightly different guidelines for bridging studies but also

have formally announced the implementation of regulatory requirements for bridging studies. For example, in Japan, more than 40 medicines have been approved based on a bridging strategy articulated in the ICH E5 guideline (Uyama et al., 2005).

1.3.2 Regulatory Guidelines in Asia-Pacific Region

Currently, Japan, South Korea, and Taiwan are the three regions that are more frequently demanding data on ethnical differences than others. The regulatory requirements for bridging studies adopted by the health authority of Taiwan will be described in Chapter 13. In what follows, for illustration purposes, we will focus on the regulatory guidelines for Japan and South Korea.

The Japanese government has made efforts to promote Japan's participation in global development and international clinical study. On September 28, 2007, the Japanese Ministry of Health, Labour and Welfare (MHLW) published the *Basic Principles on Global Clinical Trials* guidance related to the planning and implementation of global clinical studies. It outlines, in a question-and-answer format, the basic concepts for planning and implementing multiregional trials. By the guidelines, global clinical studies refers to studies planned with the objective of world-scale development and approval of new drugs in which study sites of a multiple number of countries and regions participate in a single study based on a common protocol and conducted at the same time in parallel. Special consideration was placed on establishing consistency of treatment effects between the Japanese group and the entire group. The Japanese MHLW provides two methods as examples for deciding on the number of Japanese subjects in a multiregional trial for establishing the consistency of treatment effects between the Japanese group and the entire group.

In 1999, the South Korean government announced the elimination of compulsory conduction of local clinical trials in South Korea as a condition of registration for products with fewer than 3 years' market experience or for products marketed only in the original developing country and simultaneously introduced in bridging studies. In June 2001, the South Korea Food and Drug Administration (FDA) adopted the bridging concept. The need for a bridging study would always have to be assessed, since applying foreign clinical data directly to the Korean population might raise problems due to ethnical differences. Studies on Koreans living in South Korea are required. Data generated on Asians of other nationalities may not be accepted. However, there may be instances where bridging study requirements could be exempted. In Korea, there are seven bridging waiver categories: (1) orphan (or former orphan) drugs, (2) drugs for life-threatening disease or AIDS, (3) anticancer therapy for no standard therapy or therapy after failure of a standard therapy, (4) new drugs for which clinical trials have been conducted

on Koreans, (5) diagnostic or radioactive drugs, (6) topical drugs with no systemic effect, and (7) drugs that have no ethnic differences.

1.4 Current Issues

1.4.1 Criteria for Similarity

Although the ICH E5 guideline establishes the framework for the acceptability of foreign clinical data, it does not clearly define the similarity in terms of dose response, safety, and efficacy between the original region and a new region. In practice, similarity is often interpreted as *equivalence* or *comparability* between the original region and the new region. However, there is no universal agreement regarding similarity. In addition, it is not clear how similar is considered similar and what degree of similarity is considered acceptable for regulatory approval.

Shih (2001) interpreted similarity as *consistency* among study centers by treating the new region as a new center of multicenter clinical trials. Under this definition, Shih proposed a method for assessment of consistency to determine whether the study is capable of bridging the foreign data to the new region. Alternatively, Shao and Chow (2002) proposed the concepts of *reproducibility* and *generalizability* probabilities for assessing bridging studies. If the influence of the ethnic factors is negligible, then we may consider the reproducibility probability to determine whether the clinical results observed in the original region are reproducible in the new region. If there is a notable ethnic difference, the concept of generalizability probability can be used to determine whether the clinical results in the original region can be generalized in a similar but slightly different patient population due to the difference in ethnic factors. In addition, Chow, Shao, and Hu (2002) proposed to assess similarity by analysis using a *sensitivity index*, which is a measure of population shift between the original region and the new region. Along these lines, Hung (2003) and Hung, Wang, Tsong, Lawrence, and O'Neil (2003) considered the assessment of similarity based on testing for *noninferiority* based on bridging studies conducted in the new region compared with those previously conducted in the original region. This method, however, leads to the argument regarding the selection of a noninferiority margin (Chow and Shao, 2006).

Under different interpretations of similarity, several methods have been proposed in the literature. For example, Liu, Hsueh, and Chen (2002) used a hierarchical model approach to incorporating the foreign bridging information into the data generated by the bridging study in the new region. Lan, Soo, Siu, and Wang (2005) introduced weighted Z-tests, in which the weights may depend on the prior observed data for the design of bridging studies.

Alternatively, Liu, Hsiao, and Hsueh (2002) proposed a Bayesian approach to synthesize the data generated by the bridging study and foreign clinical data generated in the original region for assessment of similarity based on superior efficacy of the test product over a placebo control. Even if both regions have positive treatment effect, their effect sizes might in fact be different. Liu, Hsueh, and Hsiao (2004) therefore proposed a Bayesian noninferiority approach to evaluating bridging studies. However, the results of the bridging studies using these Bayesian approaches will be overwhelmingly dominated by the results of the original region due to an imbalance of sample sizes between the regions. Hsiao, Hsu, Tsou, and Liu (2007) therefore proposed a Bayesian approach with the use of mixed prior information for assessing the similarity between the new and original region based on the concept of positive treatment effect. For Bayesian methods, the foreign clinical data provided in the CCDP from the original region and those from the bridging study in the new region were not generated in the same study and are not internally valid. Therefore, a group sequential method (Hsiao, Xu, and Liu, 2003) and a two-stage design (Hsiao, Xu, and Liu, 2005) were proposed to overcome the issue of internal validity.

1.4.2 Sample Size Estimation and Allocation

Recently, the trends of clinical development in Asian countries and clinical trials conducted in Europe and the United States have simultaneously been speedily on the rise. In particular, Taiwan, South Korea, Hong Kong, and Singapore have already had much experience in planning and conducting multiregional trials.

The Japanese government has also made efforts to promote Japan's participation in global development and international clinical study. As mentioned, the Japanese MHLW has published guidelines related to planning and implementing global clinical studies. In the ICH E5 "Guidance for Industry Questions and Answers" (ICH, 2006), Q11 discusses the concept of a multiregional trial and states, "It may be desirable in certain situations to achieve the goal of bridging by conducting a multi-regional trial under a common protocol that includes sufficient numbers of patients from each of multiple regions to reach a conclusion about the effect of the drug in all regions" (p. 6). Both guidelines have established a framework on how to demonstrate the efficacy of a drug in all participating regions while also evaluating the possibility of applying the overall trial results to each region by conducting a multiregional bridging trial. Recent approaches for sample size determination in multiregional trials developed by Kawai, Stein, Komiyama, and Li (2008); Quan, Zhao, Zhang, Roessner, and Aizawa (2010); and Ko, Tsou, Liu, and Hsiao (2010) are all based on the assumption that the effect size is uniform across regions. For example, assume that we focus on the multiregional trial for comparing a test product and a placebo control based on a continuous efficacy endpoint. Let X and Y be some efficacy responses for patients

receiving the test product or the placebo control, respectively. For convention, both X and Y are normally distributed with variance σ^2. We assume that is known, although it can generally be estimated. Let μ_T and μ_P be the population means of the test and placebo, respectively, and let $\Delta = \mu_T - \mu_P$. Assume that effect size (Δ/σ) is uniform across regions. The hypothesis of testing for the overall treatment effect is given as

$$H_0{:}\Delta \le 0 \text{ versus } H_a{:}\Delta > 0$$

Let N denote the total sample size for each group planned for detecting an expected treatment difference $\Delta = \delta$ at the desired significance level α and with power of $1 - \beta$. Thus,

$$N = 2\sigma^2 \left\{ \left(z_{1-\alpha} + z_{1-\beta} \right) / \delta \right\}^2$$

where $z_{1-\alpha}$ is the $(1-\alpha)$th percentile of the standard normal distribution. Once N is determined, special consideration should be placed on the determination of the number of subjects from the Asian region in the multiregional trial. The selected sample size should be able to establish the consistency of treatment effects between the Asian region and the regions overall. Let D_{Asia} be the observed treatment effect for the Asian region and D_{All} the observed treatment effect for all regions. Given that the overall result is significant at α level, we will judge whether the treatment is effective in the Asian region by the following criterion:

$$D_{Asia} \ge \rho\, D_{All} \text{ for some } 0 < \rho < 1 \tag{1.1}$$

Other consistency criteria can be found in Uesaka (2009) and Ko et al. (2010). Selection of the magnitude, ρ, of consistency trend may be critical. All differences in ethnic factors between the Asian region and other regions should be taken into account. The Japanese MHLW suggests that ρ be 0.5 or greater. However, the determination of ρ will be and should be different from product to product and from therapeutic area to therapeutic area. For example, in a multiregional liver cancer trial, the Asian region can definitely require a larger value of ρ, since it will contribute more subjects than other regions. To establish the consistency of treatment effects between the Asian region and the entire group, it is suggested that the selected sample size should satisfy that the assurance probability of the consistency criterion in Equation 1.1, given that $\Delta = \delta$ and the overall result is significant at α level, is maintained at a desired level, say, 80%. That is,

$$P_\delta(D_{Asia} \ge \rho\, D_{All} \mid Z > z_{1-a}) > 1 - \gamma \tag{1.2}$$

for some prespecified $0 < \gamma \le 0.2$. Here Z represents the overall test statistic.