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Applied Statistics in Biomedicine and Clinical Trials Design

Selected Papers from 2013 ICSA/ISBS Joint Statistical Meetings

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This symposium volume is dedicated to
Dr. Gang Zheng for his passion in statistics

Preface

The 22nd annual Applied Statistics Symposium of the International Chinese Statistical Association (ICSA), jointly with the International Society for Biopharmaceutical Statistics (ISBS) was successfully held from June 9 to June 12, 2013 at the Bethesda North Marriott Hotel & Conference Center, Bethesda, Maryland, USA. The theme of this joint conference was "Globalization of Statistical Applications," in recognition of the celebration of the International Year of Statistics, 2013. The conference attracted about 500 attendees from academia, industry, and governments around the world. A sizable number of attendees were from nine countries other than the USA. The conference offered five short courses, four keynote lectures, and 90 parallel scientific sessions.

The 29 selected papers from the presentations in this volume cover a wide range of applied statistical topics in biomedicine and clinical research, including Bayesian methods, diagnostic medicine and classification, innovative clinical trial designs and analysis, and personalized medicine. All papers have gone through normal peer-review process, read by at least one referee and an editor. Acceptance of a paper was made after the comments raised by the referee and editor were adequately addressed.

During the preparation of the book, a tragic event occurred that saddened the ICSA community. Dr. Gang Zheng of the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) lost his battle with cancer on January 9, 2014. An innovative and influential statistician, Dr. Zheng was also a dedicated permanent member of the ICSA, a member of many ICSA committees, including the ICSA Board of Directors from 2008 to 2010. We would like to dedicate this entire volume to Dr. Gang Zheng, a great colleague and dear friend to many of us!

The completion of this volume would not have been possible without each of the contributing authors. We thank them for their positive responses to the volume, their willingness to contribute, and their persistence, patience, and dedication. We would also like to thank many referees for spending their valuable time to help review the manuscripts. Last, but not least, we thank Hannah Bracken of Springer for her wonderful assistance throughout the entire process of completing the book.

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In Memoriam: Gang Zheng (May 6, 1965–January 9, 2014)

Nancy L. Geller and Colin O. Wu

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Dr. Gang Zheng

The statistical community was deeply saddened by the death of our colleague, Gang Zheng, who lost his battle with head and neck cancer on Thursday, January 9th. Gang received his BS in Applied Mathematics in 1987 from Fudan University in Shanghai. After serving as a teaching assistant at the Shanghai 2nd Polytechnic University, he emigrated to the USA in 1994 and received a master's degree in mathematics at Michigan Technological University in 1996. He then gained admission to the Ph.D. program in statistics at The George Washington University and received his P h.D. in 2000. Immediately, he joined the Office of Biostatistics Research at the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH), where he remained until his death. From his interview seminar in early 2000, it was clear that the topic of his thesis, Fisher information and its applications, was an area in which he could pursue research for many years. What was not obvious then was how prolific his research would become.

Over the past 13 years since he got his Ph.D., Gang collaborated with many researchers in developing statistical methods, including his colleagues at NHLBI, statisticians from other NIH institutes, and statistical faculty from universities in the USA and other countries. He was one of the most productive researchers in biostatistics and statistics at NIH.

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Gang developed new statistical procedures, which were motivated from his consultations at NHLBI, and published methodology papers, in which principal investigators (PIs) of NHLBI or NHLBI-funded studies became his co-authors. One example is Zheng et al. (2005), in which he developed new methods for sample size and power calculations for genetic studies, taking into account the randomness of genotype counts given the allele frequency (the sample size and power are functions of the genotype counts). Dr. Elizabeth Nabel, the former director of NHLBI, and her research fellow were co-authors on that paper. Another example is his consultation with Multi-Ethnic Study of Atherosclerosis (MESA) and Genetic Analysis Workshop (GAW16) with his colleagues Drs. Colin Wu, Minjung Kwak, and Neal Jeffries. The studies contain data with outcome-dependent sampling and a mixture of binary and quantitative traits; for example, the measurements of a quantitative trait of all controls were not available. He developed a simple and practical procedure to analyze pleiotropic genetic association with joint binary (case-control) and continuous traits (Jeffries and Zheng 2009; Zheng et al. 2012; Zheng et al. 2013).

Most of Gang's research focused on three subject areas: (1) robust procedures and inference with nuisance parameters with applications to genetic epidemiology; (2) inference based on order statistics and ranked set sampling; and (3) pleiotropic genetic analysis with mixed trait data. Although he only started working on the last subject area in late 2012, he had already jointly published four papers in genetic and statistical journals (Li et al. 2014; Yan et al. 2013; Wu et al. 2013; Xu et al. 2013), and these results built a foundation for evaluating genetic data from combined big and complex studies.

His first paper in genetics dealt with applying robust procedures to case-control association studies (Freidlin et al. 2002). This paper has been cited over 160 times, according to the ISI Web of Science (Jan, 2014). It has become the standard robust test for the analysis of genetic association studies using a frequentist approach. The SAS JMP genomics procedure outputs the p-value of a robust test of Freidlin et al. (2002) (JMP Life Science User Manual 2014). Stephens and Balding (2009) mentioned the lack of an analogous robust test of Freidlin et al. (2002) for a Bayesian analysis. In 2010, an R package, RASSOC, for applying robust and usual association tests for genetic studies was developed by him and his co-authors (Zang et al. 2010).

In addition to novel applications of existing robust procedures to case-control genetic association studies, he developed several new robust procedures for genetic association studies. In Zheng and Ng (2008), he and his co-author used the information of departure from Hardy-Weinberg proportions to determine the underlying genetic model and incorporated genetic model selection into a test of association. Other robust procedures that he developed include Zheng et al. (2007) on an adaptive procedure, Joo et al. (2009) on deriving an asymptotic distribution for the robust test used by the Wellcome Trust Case-Control Consortium (The Welcome Trust Case Control Consortium (WTCCC) 2007), and Kwak et al. (2009) on robust methods in a two-stage procedure, so that the burden of genotyping can be reduced. Gang and his collaborators wrote an excellent tutorial on robust methods for linkage and association studies with the three most common genetic study designs (Joo et al. 2010). Kuo and Feingold (2010) discussed several robust procedures developed by Gang

and his collaborators, including Freidlin et al. (2002) and Zheng and Ng (2008), and compared the power of robust tests with other tests under various situations. So and Sham (2011) reviewed and discussed many robust procedures developed by Gang, and also extended some of his procedures by allowing adjustment for covariates.

Gang developed an adaptive two-stage procedure for testing association using two correlated or independent test statistics with K. Song and R.C. Elston (Zheng et al. 2007). His adaptive procedure was used by other researchers to design optimum multistage procedures for genome-wide association studies (e.g., Pahl et al. 2009; Won and Elston 2008). His use of two independent test statistics sequentially in Zheng et al. (2007) was also used by others as one of the methods to replicate genetic studies (Murphy et al. 2008; Laird and Lange 2009). Gang also wrote an important review article with R.C. Elston and D.Y. Lin on multistage sampling in human genetics studies (Elston et al. 2007).

In 2012, Dr. Zheng and his collaborators published a book entitled "Analysis of Genetic Association Studies" with Springer (Zheng et al. 2012). It has over 436 pages with 40 illustrations. In the preface it states that "... both a graduate level textbook in statistical genetics and genetic epidemiology, and a reference book for the analysis of genetic association studies. Students, researchers, and professionals will find the topics introduced in Analysis of Genetic Association Studies particularly relevant. The book is applicable to the study of statistics, biostatistics, genetics, and genetic epidemiology." Unlike other books in statistical genetics, Zheng et al. (2012) also covers technical details and derivations that most other books omitted. In 13 years, Gang made a vast number of important contributions to statistical genetics.

In his early research (originating from on his Ph.D. thesis but extended considerably), Gang made important and extensive contributions to the computation and applications of Fisher information in order statistics and ordered data. In Zheng (2001), he characterized the Weibull distribution in the scale-family of all life time distributions in terms of Fisher information contained Type II censored data and a factorization of the hazard function, which motivated further investigations by other researchers. For example, Hofmann et al. (2005) extended his results using the Fisher information contained in the smallest order statistic. In a discussion paper by N. Balakrishnan (2007), these results were also reviewed. Some of his work on Fisher information in order statistics has been extended to Fisher information in record values (e.g., Hofmann and Nagaraja 2003) and progressive censoring (e.g., Balakrishnan et al. 2008).

Gang studied where most Fisher information is located in samples from a location-scale family of distributions, and provided theory and insight which explain why the tail and middle portions of the ordered data are most informative for the scale and location parameters, respectively. This added insight into an area initiated by the late John Tukey in the later part of the 1960s. Interestingly, this is not true for the Cauchy distribution (Zheng and Gastwirth 2000, 2002). The latest version of the classical book "Order Statistics" 3rd ed. by H. A. David and H. N. Nagaraja (2003) added a new section on Fisher information in order statistics (Sect. 8.2), which cites six papers Gang wrote on Fisher information in order statistics.

Applying his results, Sen et al. (2009) proposed a novel study design for quantitative trait locus by oversampling the informative tails of the distribution identified in Zheng's papers. Ranked set sampling is a very useful alternative to random sampling, and still an active research area, but lacked applications beyond field studies or agriculture. Gang and his collaborators applied ranked set sampling to genetics association and linkage studies, which led to two important papers (Chen et al. 2003; Zheng et al. 2006). Their work motivated many further contributions from others, including David Clayton (Wallace et al. 2006) and Danyu Lin (Huang and Lin 2007).

A very important editorial contribution by Gang is his guest editorship for a special issue on statistical methods of genome-wide association studies for Statistical Science, co-edited with Prof. Jonathan Marchini and Dr. Nancy Geller (Zheng et al. 2009). The special issue, which was published in November 2009, consists of 12 contributions from leading statisticians in the area. An introduction of this special issue appeared in the March 2010 IMS Bulletin (Zheng et al. 2010). The three editors were responsible for writing the proposal to the Editors of Statistical Science, identifying suitable contributors, and getting their agreement to participate. The executive editor, David Madigan, of Statistical Science, assigned Dr. Zheng to be the editor to handle the review process for all the submissions, except his own.

From the time of his arrival, Dr. Zheng was a statistical consultant on the design and analysis of many NHLBI-sponsored studies of cardiovascular diseases and asthma. One important project was the genetic study of in-stent restenosis, which started in 2004. With his colleagues Drs. Jungnam Joo (now at Korean National Cancer Center) and Nancy Geller, he designed this study, which was later expanded to the first genome-wide association study (GWAS) carried out by NHLBI in 2005, before NHLBI started funding GWAS. The original paper was published in Pharmacogenomics (Ganesh et al. 2004). In this study, he determined statistical procedures for quality control and developed methods for the analysis of the data. His early research in GWAS earned him invitations to present his work at the 2007 JSM, at a seminar series of the Washington Statistical Society (2007), and at a seminar series at the Department of Biostatistics at the University of Pennsylvania (2008).

In 2004, Dr. Zheng became a statistical consultant for an NHLBI study: "A Case-Control Etiologic Study of Sarcoidosis" (ACCESS). A paper of ACCESS Research Group claimed that there was no association between immunoglobulin gene polymorphisms and sarcoidosis among African Americans (Pandey et al. 2002). A routine two-degree-of-freedom test built in SAS was applied by ACCESS investigators to analyze the data. He and his colleague developed a new efficiency robust procedure with constrained genetic models for the ACCESS data and re-analyzed the genetic association. They found that it was statistically significant with the new procedure. The improvement came after incorporating the constraints on the genetic models but the routine chi-squared test ignores the restriction of the genetic model space. This research brought attention not only from the original PIs but also from the Steering Committee and the Data Safety and Monitoring Board of ACCESS. After more than 6 months of discussions in several Steering Committee meetings and consultation with a medical researcher outside of ACCESS, also under the pressure and objection from the original authors, the Steering Committee members finally voted to clear

submission of Dr. Zheng's research for publication, which appeared in Statistics in Medicine (Zheng et al. 2006). The ACCESS Research Group also decided to include this paper as an ACCESS publication. Dr. Lee Newman (Ex Officio of ACCESS and Professor of Medicine at Colorado School of Public Health) later invited Dr. Zheng to give a presentation based on his research findings.

When analyzing the data from his consultation for medical publications at NHLBI, Dr. Zheng not only developed more powerful statistical methods for the unique data, but also applied more appropriate tests to the data analysis. In one ongoing NHLBI intramural research to analyze association of candidate markers in osteoprotegerin with clinical phenotypes and its effects on cell biology in lymphangioleiomyomatosis, the original analyses were done by a staff scientist using some statistical tools built in Excel. Associations were tested using an allele-based test by comparing allele frequencies, and a genotype-based test by comparing genotype frequencies. Both results are reported. Although this is fine after correcting for multiple testing for two tests, Gang employed a method newly developed by him and his colleagues (Joo et al. 2009) to this dataset with the same allele-based and genotype-based tests, but instead of applying the Bonferroni correction for the two tests, he applied a more powerful approach to find p-values using the joint distribution of the two tests.

In addition to research contributions, Gang served as an associate editor of Statistics and Its Interface and co-edited several issues of the journal, the current one and an earlier one in honor of his thesis adviser Joe Gastwirth. He served as a referee for 43 journals and volumes, including JASA, Biometrics, Biometrika, Annals of Human Genetics, American Journal of Human Genetics, and Statistics in Medicine.

Gang's degree of productivity was extremely rare and unusually versatile. He was honored for his work by election in 2005 as Fellow of the International Statistical Institute. He also gave a large number of invited talks, demonstrating the appreciation of his work by others.

One might think that such a productive researcher would be highly competitive. In fact, the opposite was true for Gang. He was an intellectually generous and nurturing colleague. He mentored new members of the Office of Biostatistics Research at NHLBI both in research and collaboration. He also mentored predoctoral fellows and served as a Ph.D. advisor to six students (two in China and four at George Washington University). In each case, he published joint papers with these students. There was an old e-mail about one of them in which he said, "This is one of the things that makes me happy. This was a fine Ph.D. student. I gave him three topics for his Ph.D. thesis and he worked out five papers. I actually turned down authorship on the last two papers because I wanted him to come into my world and come out of it independently."

He has been equally generous to his other colleagues. We learned very quickly that if Gang asked you to collaborate with him on a research paper, to just say yes and be prepared to rearrange your own priorities so that you had time to work on it immediately, for the paper he was proposing would get written quickly, with or without your input. Indeed, Gang collaborated with almost all of his colleagues in the Office of Biostatistics Research. It was our pleasure to collaborate with him on nearly

20 papers between us. His efficiency and creativity were marvelous and inspiring. He was truly an intellectual leader in the Office of Biostatistics Research.

Gang also contributed admirably to the statistical profession by undertaking significant editorial responsibilities, serving on organizing and program committees of many meetings as well as organizing many sessions at various statistical meetings. He was also a member of the ASA Noether Award Committee. These activities illustrate Gang's generosity as a colleague and his dedication to the profession. Despite the setback of his illness, he continued to be highly productive and published seven new papers in 2013.

Gang's efficiency, creativity, and generosity were truly inspiring. Those of us who have been his colleagues and collaborators will always remember the experience. He will be sorely missed.

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Part I
Bayesian Methods In Biomedical Research

Chapter 1
An Application of Bayesian Approach for Testing Non-inferiority Case Studies in Vaccine Trials

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Abstract Non-inferiority designs are often used in vaccine clinical trials to show a test vaccine or a vaccine regimen is not inferior to a control vaccine or a control regimen. Traditionally, the non-inferiority hypothesis is tested using frequentist methods, e.g., comparing the lower bound of 95 % confidence interval with a pre-specified non-inferiority margin. The analyses are often based on maximum likelihood methods. Recently, Bayesian approaches have been developed and considered in clinical trials due to advances in Bayesian computation such as Markov chain Monte Carlo (MCMC) methods. Some of the advantages of using Bayesian methods include accounting for various sources of uncertainty and incorporating prior information which is often available for the control group in non-inferiority trials. In this chapter, we will illustrate the use of Bayesian methods to test for non-inferiority with real examples from vaccine clinical trials. Consideration will be given to issues including the choice of priors or incorporating results from historical trial, and their impact on testing non-inferiority. The pros and cons on using Bayesian approaches will be discussed, and the results from Bayesian analyses will be compared with that from the traditional frequentist methods.

1.1 Introduction

The purpose of a non-inferiority test is to show that a test treatment is "similar" to an active control for which effectiveness has been established. It is known that non-inferiority cannot be concluded from a non-rejection of a null hypothesis of superiority between test treatment and active control (Blackwalder 1982). To test

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for non-inferiority, we need to show that the effect of the test treatment is within a certain pre-specified amount of the effect of the active control. This pre-specified quantity, called the non-inferiority margin, has to be determined and agreed upon by the sponsor and regulatory agencies.

For a continuous response, suppose θ_T and θ_C are the treatment effects for test and control, respectively. Assuming a large value represents a better efficacy, a non-inferiority hypothesis can be formulated as follows:

Null hypothesis $H_0 : \theta_T - \theta_C \leq -\delta$ versus

Alternative hypothesis $H_1 : \theta_T - \theta_C > -\delta$

where $-\delta$ is a pre-specified non-inferiority margin. This fixed margin is often chosen such that by rejecting the null hypothesis, we can conclude that the test treatment will preserve certain amount of the treatment effect of the control, or the effect of the test treatment is not worse than the active control by the amount of δ. It may be difficult and sometimes controversial on how to choose the margin, but in general, the margin should be a negligible difference in clinical benefit between the two treatment groups. There are many researches and discussions on how to choose a non-inferiority margin in the literature. Some general guidelines and related references can be found in the regulatory guidance documents for non-inferiority studies (EMEA 2005 and US FDA 2010).

The non-inferiority hypothesis is conventionally tested using frequentist methods, where p value and confidence intervals for treatment difference (test treatment minus control) are calculated based on the observed data from the study. Some commonly used frequentist methods for non-inferiority tests can be found in Wang et al. (2006). For example, maximum likelihood methods are commonly used to obtain the estimate of the treatment difference and its 95 % confidence interval. The null hypothesis is rejected if the lower bound of the confidence interval for the treatment difference is greater than the pre-specified non-inferiority margin, $-\delta$. In the frequentist methods, prior information besides the current study is not utilized.

Recently, Bayesian approaches have been developed and considered in clinical trials due to advances in Bayesian computation such as Markov chain Monte Carlo (MCMC) methods. With a non-informative prior, the Bayesian approaches often produce similar results as that from the frequentist methods. One of the important advantages for Bayesian methods is the ability to incorporate prior information which is often available for the control group in non-inferiority trials. Gamalo et al. (2011) showed that the incorporation of prior information through the use of Bayesian methods may improve the power for non-inferiority tests. Here, we will illustrate the use of Bayesian methods to test non-inferiority with two real examples from vaccine clinical trials.

This chapter is organized as follows: Section 1.2 describes the vaccine studies and frequentist statistical methods and results. Section 1.3 presents Bayesian approaches including how to construct the prior distributions from a historical study, and discusses the impact of the choice of prior on the analysis results. Section 1.4 provides conclusions and discussions.

1.2 Vaccine Studies and Results from Frequentist Methods

We consider two vaccine clinical trials. To maintain some confidentiality, we will simply call them study I and study II without disclosing the names of studies and the test vaccine. Both studies are phase III double-blind, randomized multicenter trials to evaluate the safety, tolerability, and immunogenicity of a test vaccine administered concomitantly versus non-concomitantly with an influenza virus vaccine (in study I), or with PNEUMOVAX^{TM} 23 (in study II).

In each of these studies, subjects were randomly assigned to either the concomitant use group (receiving the test vaccine and the concomitant vaccine together) or non-concomitant use group (receiving the test vaccine and the concomitant vaccine separately, approximately a month apart). We will consider the non-concomitant group as the control group in the following discussions. Antibody titers were measured at baseline and approximately 4 weeks postvaccination. One of the primary objectives was to show that the antibody response to the test vaccine in the concomitant use group was non-inferior to that in the control group. The statistical hypothesis is H_0: GMT1/GMT2 ≤ 0.67 versus H_1: GMT1/GMT2 > 0.67, where GMT1 and GMT2 are the geometric mean titer (GMT) for the test vaccine in concomitant use group and that in the control group, respectively. The value of 0.67 is the pre-specified non-inferiority margin, which corresponds to a no more than 1.5-fold decrease in the GMT of the concomitant use group compared with the control group (Kerzner et al. 2007). In the statistical analyses, a natural log transformation was applied to the antibody titer. Therefore, the non-inferiority test was based on treatment mean difference in log antibody titer with a fixed margin of log(0.67).

1.2.1 Traditional Frequentist Methods

In the original trial designs, both studies were analyzed using a frequentist approach. For the primary analysis, a constraint longitudinal data analysis (cLDA) model proposed by Liang and Zeger (2000) was used. The model included natural log transformed baseline and postvaccination antibody titers as response variables. The covariates in the analysis model included treatment indicator, age at randomization, visit, and treatment by visit interaction. For study I, an indicator for region (USA vs. EU) was also included to designate the sites in the USA and European countries.

The cLDA model assumes that baseline and postvaccination values have a joint multivariate normal distribution. An unstructured covariance matrix was used to account for within subject correlation between baseline and postvaccination responses. The baseline means were constrained to be the same between two treatment groups in this cLDA model, which is reasonable due to randomization. Specifically, suppose Y_{i0} and Y_{i1} are the log titers observed at baseline and postvaccination for subject i,

then the cLDA model under a bivariate normal distribution may be formulated as

$$\begin{aligned}
&\begin{pmatrix} Y_{i0} \\ Y_{i1} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_{i0} \\ \mu_{i1} \end{pmatrix}, \Sigma\right) \\
&\mu_{i0} = \beta_0 + \beta_1{}^{*} age_i + \beta_2{}^{*} region_i \\
&\mu_{i1} = \beta_0 + \beta_1{}^{*} age_i + \beta_2{}^{*} region_i + \gamma_0 + \gamma_1{}^{*} trt_i
\end{aligned} \tag{1.1}$$

where age_i represents the age of subject at randomization, trt_i represents the treatment indicator (1 for the concomitant group and 0 for the control group), $region_i$ represents the region indicator (1 for the USA and 0 for Europe), and Σ is an unstructured covariance matrix. The factor region is used for study I only. To make parameterization simpler, we used the centralized values for age and region in the analysis. So β_0 is the mean baseline response for study population, γ_0 is the change from baseline at postvaccination for control group, and γ_1 is the treatment difference between treatment and control group. All these parameters are on the log-transformed titer scale.

This cLDA model will compare the postvaccination antibody titers between the two treatment groups while adjusting for baseline antibody titer in the presence of incomplete data. In the event that there were no missing data, the estimated treatment difference from the cLDA model would be identical to that from a traditional analysis of covariance (ANCOVA) model (Liu et al. 2009). This cLDA model can be fit using the MIXED procedure in statistical analysis system (SAS Institute Inc. 2012).

1.2.2 Analysis Results from Frequentist Method

Suppose $\hat{\gamma}_1$ and $(\hat{\gamma}_{1L}, \hat{\gamma}_{1U})$ are the point estimate and 95 % confidence interval for γ_1, then we will claim non-inferiority if the lower bound of the 95 % confidence interval (CI) is larger than the non-inferiority margin, i.e., $\hat{\gamma}_{1L} > \log(0.67)$, or the lower bound CI of the GMT ratio, i.e., $\exp(\hat{\gamma}_1)$, is greater than 0.67.

Table 1.1 presents the analysis results for both studies based on the cLDA model. The conclusions from the analyses are that: Study I met the non-inferiority criterion and concluded that the antibody response induced by the test vaccine when administered concomitantly with influenza vaccine was similar (non-inferior) to that induced by the test vaccine administered alone. However, study II did not meet the non-inferiority criterion, which indicated that the antibody response in the concomitant use group would be inferior to that in the non-concomitant use group.

It will be interesting to investigate how Bayesian analysis may help and/or alter the analysis results for these two vaccine trials. Here, we apply Bayesian methods retrospectively for illustration in these two studies, recognizing that the frequentist cLDA model was the pre-specified analysis method in the protocol.

1.3 Bayesian Approach

1.3.1 Non-informative Prior

We first consider a non-informative prior for all parameters in the cLDA model (1.1). To have better mixture in the MCMC sampling, we use conjugate prior distributions for all parameters. That is, for location parameters $\beta_{0,}\beta_{1,}\beta_{2,}\gamma_{0,}$ and γ_1, we use normal priors with a mean of 0 and a large variance to reflect uncertainty (variance = 10,000 is used in the analysis models presented below). For the variance matrix Σ, we use an inverse Wishart prior with a degrees of freedom of 2 and a very small precision parameter (0.0001 is used in the analysis models below).

The results from 5000 MCMC samples (SAS PROC MCMC with the number of MCMC iterations (nmc) = 50,000 and thin = 10 options; SAS Institute Inc. 2012) are presented in Table 1.2. It can be seen that the results are almost identical to that from the frequentist method (Table 1.1). This is as expected because the posterior distribution under the non-informative prior is essentially the likelihood function. So the estimates and credible intervals from the Bayesian analysis would be very similar to that from the frequentist analysis.

1.3.2 Prior Based on Historical Data

At the time these two trials were conducted, a historical placebo controlled trial was completed in which the test vaccine was given non-concomitantly with other vaccines. Therefore, the antibody responses from this historical trial can provide good prior information for the control group in study I and study II.

Based on the historical trial, we construct prior distributions for the baseline mean β_0, the change from baseline at postvaccination γ_0 for the control group, and the variance covariance matrix Σ for the log titers at baseline and postvaccination. Using the data from the historical trial, we obtained

$$\begin{aligned}
&\beta_0 \sim N(mean = 5.6400, sd = 0.04051),\\
&\gamma_0 \sim N(mean = 5.228, sd = 0.02937),\\
&\Sigma \sim invWishart\left(df = 2, S = \begin{pmatrix} 1.91 & -1.50 \\ -1.50 & 2.27 \end{pmatrix}\right).
\end{aligned} \tag{1.2}$$

Table 1.1 Non-inferiority analysis results from cLDA models

Study	$\hat{\beta}_0(SE)$	$\hat{\gamma}_0(SE)$	GMT ratio (CI)	Conclusion[a]
I	5.557 (0.041)	0.833 (0.041)	0.93 (0.84, 1.03)	Similar
II	5.134 (0.045)	1.059 (0.052)	0.70 (0.61, 0.80)	Not similar

SE standard error, *cLDA* constraint longitudinal data analysis, *GMT* geometric mean titer, *CI* confidence interval

[a]Similar (i.e., non-inferior) if the lower bound CI is greater than 0.67