Bulletin

July 2002
編者的話：

會刊是我們會員的主要交流園地，預計每年在一月及七月發行兩期，希望各位踊躍賜稿。文章以一至二頁為主，須用中文繁體字或英文書寫，文章性質以一般性非專門學術的文章為主，以前或本期會刊內的各篇短文都是很好的範例。稿件如採用，我們希望能由作者安排打字，完稿的上下左右邊（margin）至少要有四分之三英吋，頁碼離底邊二分之一英吋，打字打在8"x11"的白紙上。為統一起見，若以英文書寫，請用Microsoft Word打字，中文繁體字請用Microsoft Word with Valupack Farcast feature打字。稿件的截止日期是六月十五日及十二月十五日。截止日期後收到的將列為下一期的稿件。

刊內附有本會的申請表（application form），其中會員動態內的著作（publication）以一年內的新作品為限。

從1994年度起本會酌收徵才廣告費一頁U.S.$200或半頁U.S.$120。

對於以上的一些構想，如果您有任何建議，請與泛華協會執行長莊易（地址見下）聯絡，以期這份刊物更為完善。

2002會刊通訊錄編輯人員
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Publication Committee
James J. Chen (Chair), I-Shou Chang
Jun Shao, Sue-Jane Wang
Ker-Chau Li, Yi Tsong

Website: http://www.icsa.org

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EXECUTIVES AND MEMBERS OF THE COMMITTEES OF ICSA 2002

EXECUTIVES

Past President: Chao Agnes Hsiung (2002)
President-elect: Zhiliang Ying (2002)
Executive director: Yi Tsong (2001-03)
Treasurer: H. M. James Hung (2001-03)

BOARD OF DIRECTORS


STANDING COMMITTEES

Program Committee:
Term of reference: to recommend conference and symposium sites, including candidates for their chairs; to recommend general policy for all meetings, subject to approval by the Board of Directors

Finance Committee:
H.M. James Hung (chair 2001-03), Xiu Chen (2001-03), Wei-Ying Yuan (2001-03)
Term of reference: to oversee the budget, and to recommend long-term financial planning, including investments of the Association’s assets, subject to approval by the Board of Directors

Nominating and Election Committee:
Term of reference: to nominate the candidates for President-elect and members of the Board of Directors

Publication Committee:
James J. Chen (Chair 2002, member 2000-03), I-Shou Chang (2001-03), Jun Shao (2002-04), Sue-Jane Wang (Bulletin), Ker-Chau Li, Yi-Chung Yao (Statistica Sinica), Yi Tsong (ex officio)
Term of reference: to oversee the publication policy of the Association and make recommendations to the Board of Directors

Constitution Committee:
Frank Shen (Chair), Shien-Chung Chow, Chien-Pai Han
Term of reference: to review the Association’s Constitution and By-Laws and prepare a revision if necessary

CURRENT COMMITTEES

Membership Committee:
Tze-Cheg Kao (Chair 2002, member 2000-02), Rongdean Chen (2001-03), Chong Gu (2000-02), Zhaohai Li (2000-02), Xufeng Niu (2000-02), Ming Tan (2001-03), Heping Zhang (2001-03), Ling Chen (2002-04), Wai-sun Chan (2002-04), Hong Kong), Chen-Hsin Chen (2002-04, Taiwan), Guo-Ying Li (2002-04, China)

Term of reference: to recruit new members and contact interested potential individuals and organizations

Fundraising Committee:
Alice Hsiun (Chair 2002, member, 2001-03), Jianping Dong (2002-02), Kang-Chao Chang (2002-02)
Term of reference: to consider fundraising drives through individuals and corporations

Public Relations Committee:
Yi Tsong (Chair, 2002, member 2000-02), Nai-ying Wang (2000-02), Shi-Yong Feng (China), Sik-Yum Lee (Hong Kong), Lang-An Li (Taiwan)
Term of reference: to contact the news media and publicize ICSA activities; to serve as a liaison between ICSA and other professional organizations such as ASA, Biometric Society for joint activities

Awards Committee:
Term of reference: to accept, evaluate, and recommend nominations for ICSA various awards

Communication Committee:
Rong Chen (Chair 2002, member 2002-04), Don Sun (Web), Hubert Chen (Listserv)
Term of reference: to evaluate the database and use of internet

Applied Statistics Symposium Committee:
William W. S. Wei (Chair), Danny Chiang, Ivan Chan, George Chao, Yuesong Chen, Alice Hsiun, Lee Huang, Frank Shen
Term of reference: to organize the Applied Statistics Symposium, 2002

Book and Journal Donation Committee:
Tze Timothy Chen (Chair)
Term of reference: to solicit book and journal donations and to arrange their delivery to universities or colleges in need

Annual Meeting Committee:
Wei-Yann Tsai (Chair 2002, member 2002-2003), Hubert J. Chen (2002), Zhiliang Ying (2002)
Term of reference: to plan, coordinate and arrange the August annual meeting, 2002

Archive Committee:
Yi Tsong (Chair 2002, Smiley Cheng, Shien-Chung Chow, Nancy Lo, Nai tee Ting
Term of reference: to plan and implement electronic archive for the Association

Strategic Committee:
Chao Agnes Hsiung (Chair 2002), Chien-Pai Han, Tze Timothy Chen, Jeff C. F. Wu, Shien-Chung Chow, Kang-Fu Cheng, Smiley Cheng, Chiao Yeh, Yau A. Chow, Jack C. Lee, Grace Yang, Jia-Yeong Tsay, James Fu, George Tao
Term of reference: to plan long-term strategies for the Association

BIOMETRICS SECTION (2002)
H. M. James Hung (Chair), Wei-Chang J. Shih (past chair), Jen-Pei Liu (Chair-elect), Shun-en Lu (secretary), Gang Li (treasurer), Frank Shen (ICSRA Representative 2000-02)
**Editor's Page**

**ICSA's Eminent Tradition**

July 04, 2002

In this issue, we highlight the success of the 2002 ICSA Applied Statistics Symposium headed by Dr. Willis Wei, our President. Instead of using the usual East Coast locations, our program committee has tried new locations since last year from Chicago, Illinois (2001) to Philadelphia, Pennsylvania (2002) and the 2003 symposium will take place in San Diego, California. We believe this new format will attract more attendance.

Following the report of the Applied Statistics Symposium, keynote speeches presented by Dr. Robert T. O'Neill and Dr. George W. William are also published for members who could not attend the meeting. We reserve a corner for discussion on clinical therapeutic bridging studies - one of the controversial issues. And, Dr. Timothy T. Chen, former president in 1999, contributed an article on "If I could do it all over again," which provides important mentoring stories and may serve as an excellent reference for some members who may have just started their statistical careers. For interested readers, be sure to check out our new puzzles in the Statistics Delight Section.

The use of pharmaco econometrics/pharmacoeconomics (PG) in drug development is increasing and its use has tremendous potential to have a positive impact on public health and health economics. This year, in addition to our regular symposium, ICSA is also co-organizing a conference entitled "Symposium on Biomedical Technology Development" to be held at the University System of Maryland, Shady Grove Center, Maryland. The symposium date is September 28-29, 2002. Meeting announcements and registration form can be found on our website.

As some of you may know, this is the last issue during my three-year term as the Editor-in-Chief, and I almost feel like saying, "WHEW!" It's been such a run. As we inherited the baton from the former editing team at the fall sprung, I feel that all of the wonderful colleagues I have worked with felt that we should do nothing less than try our best to continue that sprint, which I want to see the next team will enthusiastically continue. With members' enthusiasm and the hard work of my colleagues, I am thankful for the rewarding experience I have had reviewing all of the wonderful contributions from all you readers for the ICSA bulletin. It is of such acclaim, we often hear praising comments not only at professional meeting gatherings but also through email responses. We are delighted to receive the strong support and have really enjoyed this service to members of the ICSA.

Lastly, I have put together an "Editorial Working Committee" page in this issue to introduce you to the members of our editorial committee, whom I greatly enjoyed working with and include a short paragraph they'd like to share with ICSA members.

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**MESSAGE FROM THE PRESIDENT**

June 30, 2002

Dear ICSA Members:

The success of an organization comes from the sustained dedication of its members. This is especially true for a nonprofit organization like ICSA. Many of our members spend their evenings, weekends, and holidays working for ICSA without any compensation. For example, because of the effort and many personal sacrifices of Editor-in-Chief, Sue-Jane Wang, our members can enjoy the wonderful ICSA Bulletin. This bulletin has a size equivalent to AMSTAT NEWS but with much wider and richer coverage. During the past three years, while we were enjoying our Christmas holidays with our families, Sue-Jane was working in her office, calling people for overdue reports, and editing articles for the final printing of the Bulletin. She completes her three-year term as Editor-in-Chief at the end of this year. She really deserves a good break. We give her our salute and thank her for the exceptional work she has done.

It has been nine years since the ICSA Constitution and By-Laws were revised. To meet the Association’s changing needs, the Constitution Committee (Shein-Chung Chow, Chien-Pai Han, and Frank Shen (chair)) carefully reviewed the Constitution and By-laws and proposed several changes, published them in the January 2002 issue of the Bulletin, and invited comments from members. At the June 7 meeting, the Board approved the revisions after careful discussion. The two most important changes were the responsibilities of the Program Committee and the Finance Committee. The Program Committee is the only standing committee of ICSA that deals with meetings. However, under the previous version of the Constitution and By-Laws, it plays no role in any ICSA-related programs other than the August annual gathering at the Joint Statistical Meetings. Under the approved revision, the Program Committee will assist the Annual Meeting Committee in planning the annual meeting as well as recommend symposium and conference sites, including candidates for their chairs. The Committee also recommends general policy for all meetings. In the same spirit, the Finance Committee will not only deal with income, expenditures, and budget, but most importantly, it will also have the responsibility of long-term financial planning, including the investment of the Association’s assets.

The world is changing and new technology is developing quickly. To keep up with these new developments, we need to keep learning during our lifetime. To provide our members with the opportunity of continuing education, we have offered short courses in the annual ICSA Applied Statistics Symposium. The Association should continue the program and offer courses in even more diverse areas. In addition, under the editorship of Sue-Jane, the ICSA Bulletin published many excellent introductory and review articles on various topics. For example, the January 2002 issue of the ICSA Bulletin contained very interesting articles in pharmacoeconomics and missing data problems. I hope that our members take full advantage of these offerings.

Because of new technology, e-mail and the world wide web have become the most common and efficient communication tools. They are also the best sources for searching for information. Many organizations have actually stopped using...
FROM THE EXECUTIVE DIRECTOR

Dear Friends:

No one can argue about the fact that ICSA is a very successful association now. The association is managed with a system. Our official journal Statistica Sinica enjoyed successful recognition year after year. Our Bulletin has evolved into a periodical with high readability with a group of energetic editors with new ideas. Our international conference blends traveling fun with knowledge sharing so successfully. Our symposium enjoys steady growth every year. This year we have over 200 participants. Does anyone remember those days with about 70 participants? ICSA Applied Stat Symposium today attracts outstanding presenters in various fields.

Friends, at the time we enjoy the fruit of success, we are also looking forward to the new challenges.

In the 2002 July issue, I identified three priority projects, accounting and tax report, homepage and web service, and electronic archiving of documents. In accounting and tax report, very fortunately, James Hung (ICSAs treasurer) and I found a very experienced CPA in Ms. Li Ming Li of Rockville. With James' effort and close working relationship with Ms. Li, the accounting and tax report is under excellent control. With the expertise and effort of our Web Master Dr. Don Sun, our homepage becomes very impressive. However, electronic archiving had not exactly enjoyed much improvement. I will try to improve it.

In order to keep up with the pace of this new age of electronic communication, we need to meet the new challenges and take advantage of what the technology offers. These are a few more projects that I believe we need to work on.

1. Establish an updated e-mail system—With the ever-increasing cost of postage and labor, and the time needed to handle the mails, mailing is not the first choice as the format of information distribution. Many of the information distributions will be replaced by e-mailing in the near future. I was quite embarrassed to find out that almost one to two-thirds of our e-mail addresses were out of date during Prof. George Tiao’s campaigns for ASA president. Remember, your updating of e-mail address is crucial to the success of ICSA's information distribution.

2. Actually, the important reason of the bounced back e-mails is that there are quite a few once members who didn’t renew the membership. Among the 1500 plus entries in our directory, less than half updated their memberships. The annual reminder at the end or beginning of the year seems didn’t serve the purpose each year. I don’t quite agree with the suggestion of sending more reminding letters through the year. I believe that with good and useful products, the customers will come. Hence I am looking forward to create more membership only services such as e-journal and bulletin, electronic chat room on controversial statistical issues, etc. All these service will take time and effort to develop, but we have talented and energetic members handle the problem.

3. The annual voting has always been time pressing because of the time and effort required for printing and mail handling. We will be investigating the possibility of electronic voting once we have a healthy e-mail system.

I am looking forward to hear from you on suggestions and proposals to improve the services and the association.

Yi Tsong
MINUTES OF 2002 JUNE ICSA MEMBERSHIP MEETING

DoubleTree Hotel Guest Suites, Plymouth Meeting, PA, June 8th, 2002

Time: 5:30 PM-6:15 PM
Chair: William Wei (President)
Minutes: Yi Tseng
Attendees: About 70 ICSA Members

1. President’s Report

Prof. William Wei made announcement that the 2002 August Membership Meeting will be held on August 13 at Hilton Hotel in New York.

Prof. William Wei congratulated and thanked the participants of the successful Symposium. He introduced the members of the Symposium Program Committee, Working Committee members and student helpers and expressed sincere thanks for their commitment and dedicated efforts. He announced proudly that the number of attendees was over 200 this year.

The president reported also that Prof. George Tiao, the founding father of ICSA was at the symposium earlier (which means his symposium attendance record is 100%) and left earlier for a meeting at Atlanta, Georgia. He mentioned that Prof. George Tiao expressed his sincere thanks to the members for their efforts to support his campaign for ASA presidency. George is extremely happy for the turnout of the election result that he lost to Prof. Efron with a narrow margin of 43% to 36%.

He wanted everyone to accept the result positively as a very successful indication for ICSA member planning to run for major ASA positions in the future.

Prof. William Wei congratulated three ICSA members, Professors Joseph Gustwirth (Chair-elect, Section on Nonparametrics), Dennis Lin (Chair-elect, Section on Physical and Engineering Sciences) and Xiao-Hua Zhou (Chair-elect, Section on Statistics in Epidemiology) for their successes in elected to the positions in ASA.

2. Honor Ceremony

The following honors and certificates were given at the meeting:
- The student Award and Travel Fellowships
- ICSA Certificates of Appreciation and bonaventures for Keynote Speakers, Drs. Robert O’Neill, George Williams and Plenary Speaker, Dr. Gordon K.K. Lau
- ICSA Certificates of Appreciation for the ICSA Symposium Corporate Sponsors
- ICSA Plaque for the 2001 ICSA Applied Statistics Symposium Program Committee
- ICSA Certificates of Appreciation for the members of the 2001 ICSA Applied Statistics Symposium Program Committee, Planning Committee and Local Service Committee

3. Announcement of Future ICSA Applied Statistics Symposium

Dr. Nancy Lo announced that the 2003 ICSA Applied Statistics Symposium is to be held at University of San Diego, California with the preliminary program to be published in the July issue of ICSA Bulletin.

Dr. Yi Tseng announced also that the Board of Directors approved that the 2004 ICSA Applied Statistics Symposium be held at Washington D.C. Metropolitan Area.

Meeting was adjourned at 6:00 PM for Banquet.


William W.S. Wei
Held at Plymouth Meeting in Greater Philadelphia, Pennsylvania

The ICSA 2002 Applied Statistics Symposium was held from June 6 to 8, 2002, at Plymouth Meeting in Greater Philadelphia, Pennsylvania. The theme of the symposium was the leading edge of statistics in health sciences. Under this theme, we invited two keynote speakers, Dr. Robert O’Neill, Director of Office of Biostatistics, CDER, FDA, and Dr. George Williams, Vice President of Biostatistics and Programming, Pharmaceutical Research Institute, Bristol-Myers Squibb Co., and Vice President of ASA. They presented our symposium audience with two different but related views: one from the regulatory point of view and one from the industry point of view. Dr. Gordon Lau, Pfizer Inc., was our other plenary speaker who gave an excellent talk on adaptive design and analysis.

The first day of the symposium consisted of short courses. There were a total of 95 people registered for these four very interesting and stimulating courses: Design Considerations for Positive Late Phase Confirmatory Trials by Dr. Irving Hwang; Active Control Non-Inferiority Studies and Adaptive Analysis Methods in Clinical Trials by Dr. Sue-Jane Wang and Dr. James Hung; Statistical Approaches in Pharmacogenomics by Dr. Kimo Zerba, Dr. Shu-Pang Huang and Dr. Frank Shon; and Advanced Log-linear Models for Categorical Data with GENMOD by Prof. Daniel Zelterman.

During the next two days of the conference, technical sessions were held on various topics, including statistical considerations in evaluating patient reported outcomes, statistical data mining in early drug discovery, design and analysis of cancer trials, multiple imputations of missing values, issues and advancements in pharmaceutical statistics, statistical applications in genomic research, financial econometrics, regulatory issues in planned interim analy-
am very grateful to these dedicated committee members, including Daene Chiang, Ivan Chan, George Chao, Yisong Chen, Alice Husan, Francis Husan, Lee Huang, and Frank Shi. The symposium would not have been such a success without their dedication and sacrifices. I would also like to thank Chang-Kuei Chang, Yuning Liao, Wenjing Wang, and Brian Yen for taking photos for the symposium and Yue Chen, Shuwai Ma, Xinhuan Qin, and Sha Xuo for helping with registration.

To encourage students to participate in professional meetings, we continue to offer student awards and travel fellowships. We thank the Student Award and Travel Fellowships Committee: Weichung J. Shih (Chair), Carol Chien, and ZhiHuang Liu, and congratulate this year's winners: Zhengqiong Zhang, Jun M. Liu, and Yi-Chun Zhao. We also thank our corporate sponsors: AstraZeneca, Aventis Pharmaceuticals, Bristol-Myers Squibb Company, GlaxoSmithKline, Johnson & Johnson PRD, Merck & Co., Novartis Pharmaceuticals, Organon Inc., Pfizer Inc., Purdue Pharma, and Wyeth Consumer Healthcare. Their generous financial contributions support these student awards and many other programs in this symposium.

In closing, on behalf of the Committee, I wish to thank all short course instructors, session organizers, speakers, and participants for their contributions. Their efforts in choosing the right topics and selecting the right speakers to make outstanding presentations and conduct stimulating discussions have contributed greatly to the success of this symposium.
Banquet speaker, Judge Ida Chen, receiving a certificate and a small token of appreciation from the symposium chair, Prof. William Wei

Lunch Break at the symposium

Dinner Banquet

Dr. Daniel Zelterman, Yale University

Editorial Working Committee

Sue-Jane Wang, Ph.D.
U.S. Food and Drug Administration,
Maryland, USA

With the growing population, life follows but a central limit theorem. Outliers, too small or too large, worst or best, etc. may be considered "special" for a short while. Eventually, we live toward a bell-shaped world. "Harmonic mean" is in our heart.

C. Andy Tsao, Ph.D.
National Dong Hwa University, Taiwan

"We are faced throughout our lives with agonizing decisions, moral choices... But we define ourselves by the choices we have made. We are, in fact, the sum total of our choices. Events unfold so unpredictably, so unfairly. Human happiness does not seem to have been included in the design of creation... And yet, most human beings seem to have the ability to keep trying and even to find joy from simple things like their family, their work and from the hope that future generations might understand more."
(From Crimes and Misdemeanors, Woody Allen)

Huiliang Yang, Ph.D.
The University of Hong Kong, China

As a teacher, I want to offer my students some insight into all the interesting aspects of actuarial science. However, when not teaching, I also enjoy research and receive great pleasure out of new discoveries and being able to contribute something to the world of science.

Kao-Tai Tsai, Ph.D.
Avantis Pharmaceutical Inc.

Everyone should know as much as statisticians do but nobody should ever call himself/herself a statistician.

Statisticians are almost always at the supporting role and, therefore, are almost always under-appreciated. (Try to work with Mentally Damaged M.D. and you will know...)

Teach your children statistics but never ever encourage them to follow your footsteps unless....

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ICSABulletin
want to enjoy life along the way. So far I enjoy my 11 year old daughter and 8 year old son the most. Being able to provide them a decent growth environment and to influence them in the best possible way that I perceive, just makes me feel great.

Timothy Chen, PhD
Southwestern Baptist Theological Seminary, Texas

Life is a MCMC. Monte-Carlo is random, not haphazard. Markov chain follows a certain mechanism. Life has both random and deterministic components. But after a lifetime of MCMC, each person can build a tapestry of life with a beautiful distribution.

Ange Hsiung, PhD
National Health Research Institute, Taiwan

Life is a positive-drift random walk, filtering out noise and looking for signal.

Greg Wei, PhD
Pfizer, Inc.

"To a statistician, the reason for not to play those slot machines in the casinos is so convincing. Because it is like to prove the large number theory by running a simulation funded by your own hard-earned money. However, regardless the truthfulness of this analogy to statisticians, the real world is following a more optimistic "small number theory", that is you will gain nothing unless you do it, and you may get lucky."

Pretest leads to better solution in your life

William Wei, PhD
Temple University, PA, USA

The job of a statistician is to help people see the world through a small window.

Chien-Pai Han, PhD
University of Texas, Arlington, Texas, USA

I would like my friends regard me as a marathon goer because I keep going and I hate to lose the miles I have already accumulated. Meanwhile I do also

Keynote Speaker
Robert T. O’Neill, Ph.D.
Director, Office of Biostatistics, CDER, FDA

The management of risk associated with exposure to new drugs in the marketplace recently has been receiving considerable attention in the medical and lay literature as well as in regulatory discussions. This focus on risk management has occurred, in part, because risk management is viewed as a necessity to address the problem that over the last few years several new drug products have been withdrawn from the market place for safety reasons. The scientific community and the public in general have questioned why. It can be argued that in order to manage risk, one needs to estimate it so that risk can be communicated to patients, prescribers and the public at large. Estimation of risk encompasses statistical quantification of the risk, which involves a variety of statistical methods, concepts, data collection strategies and study designs. Because statisticians have not devoted substantially the same attention to design, analysis and interpretation of safety studies and study outcomes as they have for efficacy studies and outcomes, statisticians involvement in this area of risk assessment can benefit the risk management effort by insuring the use of more statistically appropriate methods and by increasing the level of statistical attention to the problem.

A series of published literature (1, 2, 3) by FDA and by others over concern for whether the removal of products from the market indicated a problem in the evaluation of drug safety has spurred a public discussion and a new visibility of safety assessment. Recent experiences with the removal from the market for
For example, the label of a new drug is the primary manner in which information about use of a new drug is promulgated to physicians, patients and health care providers. Among other information, the drug label contains quantitative estimates of risks of certain adverse events, their time dependencies, and in some instances, patient monitoring strategies intended to prevent or minimize the occurrence of a serious adverse event. Take for example, the WARNING section for non-steroidal anti-inflammatory drugs (NSAIDs) which states that "Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time without warning symptoms, in patients treated chronically with NSAID therapy; these appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year." This is a layman version of stating what the hazard rate is for serious gastrointestinal events (12).

Another simplistic approach that is often used in estimating rates from two or more studies is to combine the numerators and denominators of crude incidence rates from each study into a combined overall incidence rate. Without controlling for time, this approach will always underestimate the true risk. Ignoring the control for time, especially when a life table approach is applicable but ignored in favor of a crude binomial type rate, is to underestimate the width of the confidence intervals for cumulative rates, again understating the uncertainty of the estimates.

In order to fully characterize the multiplicity of adverse events and patterns of events and exposures that may be observed in a single patient in a clinical trial and subsequently to estimate event rates, relationships, and risk factors that are associated with these events, it is necessary to take a more global approach to the data contained in a patient's case record. Most medical officers, when evaluating the safety profile of a new drug, are interested in the longitudinal, chronological profile of a patient in a clinical trial. This allows one to judge the time progression of lab values from pre-treatment status to on treatment status, the censoring patterns, the multiple events of different types that may occur to an individual subject, and may even be recurring: Visual graphics, plots and related pictures of intermittent, chronological information are very useful here. For time to event data for which patients have different covariate levels related to differential event rates, there has been recent work on how to present this information so that it can be better interpreted (13). Dublin, Muller and Wang have suggested event history graphs of censored survival data. The analysis of such data from a population perspective, can be viewed as a type of event history analysis (14) in which time dependent confounders, and structural failure time models may help characterize and estimate risks that are functions of time and risk factors. Kelding (14) has proposed such approaches for observational data, which is often the form that safety data takes when single exposure cohorts are evaluated for risk assessment.

When drugs are approved and made available to patients, this phase is typically called post-market surveillance, and has a particular focus on safety evaluation. This phase of surveillance is when new drugs are in general use in large diverse populations and adverse events that are rare or that are associated with concomitant use of other drugs often are observed and reported to FDA. In this situation, the challenge is to assess whether such patterns of occurrence are real, represent causal associations, and whether any regulatory actions, like updating the label, restricting use, or market withdrawal, should be taken. The MedWatch form is the vehicle that is used to collect and report such patient level adverse events to FDA and to manufacturers. These reports can be summarized as counts and
are amenable to exploratory statistical analyses that can help signal associations worthy of more in depth evaluation or follow-up work. FDA has been exploring and developing various approaches to evaluating such data bases, which now are very large, including over two million reports and many drug—adverse event combinations. If one views the counts of all drug—adverse event combinations as a large sparse two by two table, it is possible under assumptions of independence of drugs and events to calculate expected counts, compare them to observed counts, and model the ratios of these observed to expected counts for the purposes of identifying those combinations that appear much larger than expected. This concept is behind the Bayesian data mining item association methods that DuMouchel developed for FDA to address signals of unusually high associations between drugs and adverse events (15, 16, 17). This problem becomes very complex when multiple drugs or multiple related adverse events are responsible for the higher than expected observed counts.

In some situations, only a large clinical trial whose objective is to evaluate a specific aspect of safety of a new drug will provide answers. Recently, large randomized controlled clinical trials designed and powered for safety outcomes have been conducted (18, 19). These studies present new challenges as new statistical issues are being identified for such safety focused studies. Multiple endpoints, informative treatment related censoring, time dependent surrogate markers indicative of later serious events and multiple risk factor identification are just some of the statistical issues that arise in these studies. Statisticians must contribute more to the design, analysis and interpretation of these studies in the future. When randomized studies cannot be conducted, observational epidemiological studies can be. A recent large case-control study examining the relationship between phenylpropanolamine and the risk of hemorrhagic stroke in women was conducted, published and served as the basis of a regulatory action to withdraw this drug from some uses (20). This study was an interesting example of group sequential designs being applied to a case control study.

Risk assessment, communication and management is likely to be the theme for the next decade as we deal with the management of benefit and risk for the introduction of new drugs in the marketplace. Statisticians have played a critical role in the planning, analysis and interpretation of efficacy studies, but have been much less involved in safety studies. As a result, the sophistication of safety studies and quantitative safety assessment is substantially less rigorous and developed. It is time for statisticians to contribute more to quantitative risk assessment for new drugs and to bridge the disciplines of epidemiology, clinical pharmacology and clinical trialists. Most clinical trials can also be evaluated in more depth for safety signals such as biomarkers of serious events that are observed or cause withdrawal from trials. The challenges here are exciting but must be met if we are to contribute to the future management of risk associated with exposure to pharmaceuticals.

Reference


Lazarou, J., Pomeranz, B.H., Corey, P.N., 'Incidence of Adverse Drug Reactions in Hospitalized Patients.' JAMA, 1998; Vol. 279, No. 15, 1200-1205


Mukherjee, D., Nissen, S.E., Topol, E.J., 'Risk of Cardiovascular Events Associated with Selective COX-2 Inhibitors.' JAMA, 2001; 286:954-959.


DuMouchel, W. 'Bayesian Data Mining in Large Frequency Tables, With an Application to the FDA Spontaneous Reporting System.' American Statistician. 1999, 53: 177-190.


Emerging (and Continuing) Issues for Statisticians in Drug Development from the Perspective of an Industry Statistician

The pharmaceutical industry anticipates an increasing volume of leads through technological advances in drug discovery. Clinical trials are becoming more complex in terms of the study of more complex diseases, more demanding customer information needs, and increasing number of subjects per trial. The life span of novelty of new drugs is becoming shorter. Consequently, the pharmaceutical industry is increasingly giving attention to improving the drug development process. I would suggest that in all of these changes, there is an increasingly important and expanding role of the discipline of statistics.

Pharmacogenomics and pharmacogenetics are starting to have an impact on drug discovery and drug development. Pharmacogenomics is the study of the relationships between genetic variability and drug response. Single nucleotide polymorphisms, or SNPs, are the most common form of DNA sequence variability. Associations of SNPs and other genetic variants with disease, drug response, and adverse events have been documented in the scientific literature. As noted by Roses (2001), if trials are limited to those patients with a drug-responsive SNP defined in earlier studies, then clinical trials could be performed faster, with fewer patients and less expense. This would, of course, segment the patient group for which the drug is indicated. In the areas of pharmacogenomics and pharmacogenetics, ethical and data privacy issues are fundamental.

A new technology in drug discovery allows the measurement of gene expression on a wide scale, namely microarrays. As Holder et al (2001) note, the large number of genes, multiple levels of variation, and typically small number of experimental units combine to make analysis of data from these arrays challenging. There is inherent noise associated with the assay process. Basic questions from microarray experiments include: For which genes have we detected expression? For which genes has the expression level changed between experimental conditions? As Simon et al (2002a, 2002b) note, the design and analysis of microarray experiments should be tailored to study objectives or questions. For predetermined class comparison, the objective is to establish whether gene expression profiles differ and identify genes responsible for differences. For class discovery, the objective is to discover clusters among specimens or among genes. For class prediction, the objective is to predict phenotype using information from gene expression profiles.

Contributions to these emerging areas of early phase drug discovery and development from the field of statistics include attention to such classical statistical issues as data quality, experimental design, data visualization, and analysis. In microarray experiments, as in experimentation in general, a well planned design is more likely to lead to interpretable results, and appropriate designs are dictated by particular study objectives. In terms of a specific design issue, replication is critical and yet it is recognized that the ability to replicate will be limited due to limited supply of samples, time, and resources. As one would expect with these types of experiments several traditional analysis issues exist. For example, missing values arise. As noted by Troyanskaya et al (2001), missing values occur for diverse reasons, including simply due to dust or scratches on the slide. There is not a large published literature concerning missing value estimation for microarray data, but much work has been devoted to similar problems in other fields, and these methods are now being applied to microarray data. In the case of high density arrays, for some study objectives a very large number of statistical tests will be carried out on the data. Carrying out such a large number of tests will result in an elevated false positive rate if a correction to nominal p values is not applied. To summarize these comments regarding microarrays, Holder et al (2001) note although microarrays hold great promise for helping researchers understand complex patterns of gene expression, in some ways they are not different from other assays and classical statistical issues arise.

As we move from drug discovery to clinical trials, we should at least provide one example of the contribution of statistics to drug formulation. One of the challenges of developing a formulation and process for a new chemical entity is determining whether the proposed formulation or process will be sufficiently robust for scaling from the laboratory to the factory. A standard experimental approach whereby one factor is varied and all others remain constant, will give some level of understanding of the system, but does not provide any insight into the impact of other possible variables in the system. Sophisticated experimental designs allow multiple independent variables to be studied with a limited number of batches.

Researchers and patients wish to assess the effectiveness of promising new treatments as quickly as possible. Surrogate endpoints constitute an effort to address this issue and have
received considerable attention in the medical statistical literature. The extent to which a biomarker is appropriate for use as a surrogate endpoint in evaluating a new treatment depends on the degree to which the biomarker can reliably predict the clinical benefit of that therapy as compared to a standard therapy. As pointed out by Fleming and DeMets (1996), the treatment may affect the disease process through multiple pathways. Such considerations underlie the difficulty of statistical validation of a response variable as a surrogate endpoint. While it is difficult to determine whether a laboratory measurement or physical sign can be a useful substitute for the target clinical outcome, it is still desirable to quantify the proportion of treatment effect explained by a surrogate relative to the overall net treatment effect. As Buyse et al (2000) noted, although others have expressed reservations about the validation of surrogate endpoints, in practice, the need to evaluate treatment effects as fast as possible will remain important.

Let us now turn to another area of clinical trial design, equivalence or non-inferiority trials. As Quan, Bolognese, and Yuan (2001) noted, as medical science advances, some of the focus in new drug development has been shifted to develop new medicines which may not necessarily be more effective compared to currently marketed drugs, but have some other advantages, like reducing toxicity, improving patients' comfort, or enhancing patients' convenience. As there is increased need for comparative data, active controlled clinical trials are frequently employed in equivalence or non-inferiority designs. Design and analysis issues (choice of delta, analysis set, assay sensitivity, choice of control group, quality of trial conduct) need to be carefully considered. A critical issue in the design of such trials is the definition of the margin of equivalence or "delta."

As noted by Gould (2001), interim findings of a clinical trial often would be useful for adjusting the sample size if necessary to provide the required power. Strategies for carrying out the interim examination that have been described over the past several years include internal pilot studies and blinded interim sample size adjustment. Clearly, methods not requiring unblinding the data before completion of the trial would be most appropriate. Moreover, extending a trial has its risks. The investigators/patients enrolled later in the course of a trial are not necessarily the same as those recruited early.

As noted by Berry (2001), designs of phase II and III clinical trials are usually static in that the sample size and any prescription for assigning treatment, including randomization protocols are fixed in advance. Results observed during the trial are not used to guide its course. There are some exceptions. For example, some phase II cancer trials have two stages with stopping after the first stage possible if the results are not sufficiently promising (Simon, 1989). Berry (2001) describes a family of designs that are dynamic in the sense that observations made during the trial can affect the subsequent course of the trial. Concern noted by Chi, Hung, and O'Neill (2001) are not so much the technical limitations to methodology for adaptive flexible designs as to the practical aspects of operational implementation of them so as not to introduce bias.

Analysis issues in clinical trials which will continue to require attention by statisticians include the analysis of missing data and multiplicity issues. It is interesting that we noted similar key analysis issues in drug discovery as well. Missing response data is a very common occurrence for longitudinal studies because of treatment drop out, mistimed measurements, subjects being too sick to come to the clinic to be measured, and so forth. Often, missing response data in these studies is non-ignorable in the sense that the reason for missingness often depends on the missing values themselves. As summarized by Ibrahim, Chen, and Lipsitz (2001), there is an extensive literature of methods for maximum likelihood estimation with nonignorable missing data using selection models, pattern mixture models, and conditionally linear models. Last observation carried forward (LOCF) approaches are common in the analysis of pharmaceutical clinical trials. Another issue in the analysis of clinical trials requiring continuing attention is the area of multiplicity. Multiplicity can arise in many different ways including multiple treatment groups, multiple outcome variables, multiple subgroups, and interim analyses. Approaches to the handling of these issues are critical to pre-specified in the protocol or data analysis plan before unblinding of the trial. Closed testing procedures and hierarchial procedures are some examples of approaches that are currently successfully applied.

Traditionally, much attention has been given to statistical methods for the analysis of efficacy data in clinical trials with somewhat less attention applied to safety data. Recently, specific attention is being given to the challenging issues involved in the analysis of safety data within the context of clinical trials as well as spontaneous reports of adverse drug reactions. The FDA has been investigating methods for the analysis of data collected through the spontaneous adverse experience reporting system. Specifically, data mining algorithms (e.g., DuMouchel's empirical Bayesian data mining approach) in conjunction with visual graphic displays are being considered. (DuMouchel, 1999; O'Neill and Searleman, 2001) Turning to clinical trial data, Gould (2001) notes that analysis of safety/tolerability differ fundamentally from analyses of efficacy. Tests for treatment differences in adverse event risk that had not been identified in the design of the trial present potentially serious multiplicity and interpretation issues because the outcomes generate the hypotheses. Information about safety including clinical signs and symptoms, vital signs, etc. can be expressed in a natural triage. A relatively small number of safety issues (e.g., specific adverse events or collections of them) ordinarily will be identified a priori as important and hypotheses about them can be tested like efficacy. All other events are handled primarily descriptively with the particular approach depending on their frequency. As Chang-Stein, Le, and Chen (2001) note, there are many other areas in which statisticians can assist in efforts to understand the safety profile of a pharmaceutical product. Statisticians can further develop methods for risk assessment that will facilitate benefit/risk assessment.

There is increasing interest in quality of life and other outcome data assessing patient's well being. As noted by Martin (2001), patient reported outcomes (PROs) include quality of life, functioning, symptoms, etc. Issues include the many different measures and scales both generic and disease specific, the subjective nature of such measures, and the lack of a gold standard in many cases. Scales and measures need to be validated. Statistical challenges include the multiplicity issues that arise in such a multi-dimensional context as quality of life and patient reported outcomes.

Pharmaceutical companies increasingly need
to demonstrate cost-effectiveness of its products in addition to simple effectiveness. Payers, formularies, reimbursement decision bodies, etc. are requiring health economic information. For example, in the UK, the National Institute of Clinical Excellence (NICE) has been established to address cost as well as effectiveness for treatments for the National Health Service.

Moving beyond the individual clinical trial, meta-analysis has been an important component of evidence-based medicine. Meta-analysis, or quantitative overviews, have now been applied to many areas of medicine. Meta-analysis generally results in a number representing an average treatment effect, and this has sometimes led to controversy over whether the clinical trials were similar enough with regard to treatments, populations, quality of conduct, etc. for meaningful combination.

Let us now turn our attention to other approaches for extracting information from existing data. Given the wide use of advanced data base technology and the efficient storage of huge amounts of data, there has been considerable interest in data mining approaches or Knowledge Discovery in Databases (KDD) methods. Data mining methods and algorithms include recursive partitioning (e.g., CART) and other computer intensive methods. However, it is critical that fundamental attention be given to the data quality of such data that is being analyzed and, consequently, considerable energy can be expected to be devoted to data preparation. The validity of models that are derived need to be fully tested with independent samples (e.g., the concept of training and test sets). The models need to be evaluated by domain experts (e.g., physicians) to ensure that they make sense, and, hence, conclusions are interpretable. Results of data mining activities frequently are hypothesis generating (Shnaider and Schneider, 2001).

Policy matters related to the pharmaceutical industry and statistical issues have received considerable attention recently in various forums. Specifically, the role of data safety monitoring boards has received particular attention (FDA, 2001). As Ellenberg (2001) noted, in recent years, regulators have encouraged sponsors to establish independent DMCs to monitor trials with endpoints such as mortality or other major events such as well-defined progression of a fatal or disabling disease. However, issues have arisen regarding the requirements for an independent DMC. It may be the case that individuals within a company who have been involved with the development of the product being tested have great insight into the product’s properties that could be useful to monitoring the trial. It may be efficient to have the data processed and analyzed by the statistical/data management group at the company. Hence, one or more individuals from that group will of necessity have access to the interim data in order to prepare and present the interim analysis to the DMC.

A second policy issue to consider is relative to the reporting of clinical trials. Journal editors and others have given attention to issues involved in the reporting of clinical trials and data access. As Altman et al (2001) note, there is evidence that the quality of reporting of randomized, controlled trials is less than optimal. The CONSORT standards provide a particularly helpful guideline in this regard and the application of those standards and their revisions should be encouraged. Readers should not have to speculate as to the methods used. This information should be transparent so that readers can differentiate trials with unbiased results from those with questionable results. It was noted at a recent FDA (2001) conference as well as in a policy report in the New England Journal of Medicine (Bodenheimer, 2000) that there is concern about the prompt reporting of clinical trials even negative trials.

The need for statistical excellence in drug development will not decrease. The technical skills of the statistician are required, but additionally the logical thought and attention to precision and accuracy that the statistician has are also required. Excellent communication skills are critical to the success of the statistician (Pocock, 1995). As statistical software has become increasingly available, statisticians must adapt. Given the availability of software, statisticians now are able to teach scientists and other researchers how to conduct their own routine analyses. Statisticians are freed up to conduct the more complicated or unusual analyses. Additionally, the statistician must become more efficient in providing timely information. As Waife (2001) notes, there is an assumption that all of the changes we have been discussing in the pharmaceutical industry will not be accompanied by increased levels of human resources. Hence, there will be pressure on organizations to respond with effective time and resource savings.

The training of statisticians should increasingly emphasize areas of biological research (e.g., genetics, molecular biology, and computational biology). Successful solutions in medicine will require cross-disciplinary teams to arrive at those solutions. As Tobi et al (2001) noted, research is increasingly collaborative. The biostatistician must be an integral member of the team and have a substantial involvement at early stages in the planning and design of studies. In order to contribute in such a fashion, the biostatistician must have more than a summary knowledge of the subject matter. Appropriate knowledge of the relevant epidemiology is important. However, methodological skill and research is fundamental for the statistician. The statistician must keep up with biostatistical as well as major medical literature in order to familiarize himself/herself with new techniques and ideas.

To summarize, in this review of emerging issues for statisticians in drug development, we have superficially covered many areas from drug discovery to drug development, from design to analysis, some aspects of policy, and finally the role and training of statisticians. As DeGruenella et al (2001) stated, research in biostatistics and technology is yielding promising new ways of understanding and measuring human disease processes. Genome sequencing, DNA microarrays, proteomics, and magnetic resonance imaging are giving rise to new tools of biostatistics and epidemiology that are being utilized and are producing more information than was obtained through previous methods.

It is important to note that I have commented on the need to recall basic principles of experimental design, variability, replication, testing of adequacy of models, etc. Although new technologies are becoming available to aid in drug discovery and development, we must remember to continue to value the core principles of statistical science that have been established over the last sixty years or so. As Simon (1991) noted a decade ago, "We will see many exciting medical developments but the need for statistical excellence in drug development and treatment evaluation will not decrease." It is interesting to note that one of the top ten medical developments of the past millennium was the application of statistics to medicine.
I would suggest that statistical considerations are now even more vital in clinical development than in the past.

References


Food and Drug Administration (2001) FDA Guidance on Clinical Trial Data Monitoring Committees (DMCs) Open Public Meeting 11/27/01.


Brief Biography of Candidates

CANDIDATES FOR PRESIDENT-ELECT

SHEIN, C. Frank

[PRESENT POSITION] Director, Clinical Discovery Biosciences and Data Management, Bristol-Myers Squibb Co. [FORDERER POSITIONS] Director and Associate Director, Non-clinical Biosciences, Bristol-Myers Squibb Co., 1996-2001; Manager and Biometrician, Biometrics Research, Merck & Co, 1993-1996; Research Statistician/ Sr.Statistician/Statistician, Biometrics, Wyeth-Ayerst Research, 1989-1993. [DEGREES] Ph.D., 1992, Statistics, Temple U.; M.S., 1987, Statistics, Temple U.; M.S.E., 1985, Chemical Engineering, Lamar U.; B.E., 1978, Chemical Engineering, Chang-An University, Taiwan. [FIELDS OF MAJOR STATISTICAL ACTIVITIES] Statistical collaboration or leadership in the following areas: computational chemistry and computerized data in Drug Discovery; natural product toxonomy; microbial medium optimization; psychopharmacology; pharmacokinetics; data warehousing and mining; pharmacodynamics; bioequivalence; clinical pharmacology; pharmacogenomics; catalyzing scientific research with statistical thinking. [PUBLICATIONS] “Testing Non-additivity of Biological Activity in Combinatorial Chemistry,” 2001, to be appeared at Combinatorial Chemistry & High Throughput Screening; “Binary Fetal Intervene-Based Recursive Modeling Using Multiple Atoms and Physicochemical Property Class Pair and Torsion Descriptors as Decision Criteria,” 2000, J. Chem. Inf. Comput. Sci.; “Experimental Automatism: Echopricha: The First Teleimplicant In Med Lacthax,” the NOD2 Gene,” 1998, J. of Immunology; “Robot and Bootstrap Testing Procedures for Bioequivalence,” 1994, J. of Biopharmaceutical Sci., plus 15 other authored or co-authored manuscripts in J. of Medicinal Chemistry, Arthritis and Rheumatism, SUGI Proceedings, Psychopharmacology, Pharmacology & Biochemistry & Behavior; Drug Development Research; Annuals of the NY Academy of Sciences; Fundamental and Applied Toxicology. [ICSA ACTIVITIES AND OFFICES HELD] Board of Directors (2000-2003); Chair of Constitution Committee (2001); Member of Nomination and Election Committee (2001); Long Range Financial Planning Committee (2000) and Applied Statistical Symposium Committee (2000, 2001, 1997). [RELATED PROFESSIONAL ACTIVITIES] Associate Editor, J. of Biopharmaceutical Statistics (2002-2004); PRIMA Biostatistics & Data Management Steering Committee member (2000-2003); Vice Chair, District 1, ASA Council of Chapters (2000-2002); ASA Committee on Career Development (2001-2003); Workshop chair (1999) and co-chair (1998) of the Midwest Biopharmaceutical Statistics Workshop; Symposium Chair (1995-1997) of the ASANO Chapter; Program Chair (1996-1997) of the ASA Princeton-Tucson Chapter; Co-chair (1997) of the ASANO Spring Research Conference; International Biometrics ENAR regional advisory board member (1997-1999). [STATEMENT] I am truly honored to be considered as a candidate for the President of the ICSA, and I thank the Nominating Committee for this opportunity. International Chinese Statistical Association is a vibrant organization that has grown so much with our growing profession, and I am proud to be part of its growth. Our members have become major statistical work force among industry, academia, and government in this country as well as around the world. I will also hold important offices and actively participate in other statistical societies such as ASA, ENAR/WNAR and IMS. Our Journal, Statistical Sinica, is one of the most cited statistical journal in the world. The superior program in our annual Statistical Symposium has drawn high attendance with extended duration from one day ten years ago to two and half days this year. While we can celebrate these successes, there are still challenges and issues for the ICSA to address over the next several years. We need to be more effectively in connecting and serving our members. It is our essential mission to provide our members opportunities to enhancing their technical as well as leadership skills. Our web site needs to be enhanced to better communicate information globally such as career opportunities and “e-mentor” to provide career advice. We need to increase the diversity of our membership and continue to maintain our close linkage with other statistical societies. Our Board needs to build better mutual trust so the joint efforts exceed the sum of our individual wisdom. We need to be more than just the Board members in our strategic planning in order to devise a plan that will guide us for the next five to ten years. Last but not the least, we need to nurture our own leaders in our organization.

When I attended the first ICSA Applied Statistical Symposium held in NIH in 1990, I was still a graduate student who just entered the industry and all I wanted was to be a member. When I started to get involved in organizing Applied Symposium year after year, all I wanted was to make every symposium a success and I felt so rewarding when I saw my friends and new members enjoy the conference. When I started to serve on the Board, I decided to do the best I can to sustain the quality and success that so many forerunners had contributed to. Presidency of the ICSA would be an enormous challenge to many of us. I am very appreciative of your support in my candidacy. I am looking forward to working toward the ICSA mission. I shall be fortunate if I get the support of you.

SUN, Don X.

[PRESENT POSITION] Member of Technical Staff in the Department of Applied Mathematics and Statistics at the State University of New York, Stony Brook, since 1993-1995. [DEGREES] B.S. in Applied Mathematics and M.S. in Statistics from Southeast University, China in 1989, Ph.D. in Statistics from the University of Waterloo, Canada in 1993. [FIELD OF MAJOR STATISTICAL ACTIVITIES] Dr. Sun’s main research interests include statistical design of experiments, quality engineering, signal processor and speech recognition, graphical methodology and distributed computing for analyzing massive datasets, data mining, and, in the recent few years, Internet traffic research in measurement, analysis, modeling, and network simulations. (http://csen.bell-labs.com/staff/internetTraffic) [SELECTED PUBLICATIONS] He has published over 30 papers in statistics journals including Techometrics, Journal of Quality Technology, JRSS, JASA and engineering journals including Signal Processing, IEEE Transactions on Speech and Audio Processing, and ACM Sigmetrics. Some representative articles are: “A catalogue of two-level and three-level fractional factorial designs with small runs,” 1993, International Statistical Review; “Optimal Blocking Schemes for 2^m and 2^{n-p} Designs,” 1997, Techometrics (Winner of 1998 Jack Good Memorial Prize); “Analysis of Interval Censored Data from Fractionated Experiments Using Covariance Adjustments,” 2000, Techometrics (Winner of 2000 Frank Wilcoxon prize); “On the Nonstationarity of Internet Traffic,” ACM SIGMETRICS, 2001, [ICSA ACTIVITIES AND OFFICES HELD] Dr. Sun is currently a member of the ICSA Board of Directors (2001-2003), and a member of the ICSA communications committee responsible for the ICSA web site since 1997. He developed the first ICSA applied symposium web site in 1997, and since have developed and maintained web sites for most of the ICSA applied symposia and ICSA Conferences. [RELATED PROFESSIONAL ACTIVITIES] He is a member of ASA, ASQ, ICSA, and IEEE. [STATEMENT] The fast growing information technology has generated unprecedented demands for statistics in this Internet age. It creates exciting opportunities for statisticians and the statistics discipline and profession worldwide. A major role of ICSA is to help members to take advantage of the opportunities and to build visibility for statisticians (especially Chinese statisticians) in science and technology beyond our own discipline and profession. I strongly believe that communications networking among ICSA members and with members from other professions is the key to achieving this goal. I will focus on some specifics in promoting activities and creating services that meet member's growing needs.

I would like to promote activities in career development for members, especially for the junior members who are at the beginning of their statistics career. As continuing education and learning is one of the most effective ways to make advancement in one's career path, it will be very beneficial to members for ICSA to have specialized training programs in the form of short courses, workshops, and tutorial sessions. ICSA has been providing short courses at the annual Applied Statistics Symposium, so I think we could extend this success to more ICSA sponsored satellite events of short courses and workshops at smaller scales and in different local geographical areas. This effort will not only help members in gaining new knowledge and skills, but also provide more opportunities for building a stronger network among members.

The current ICSA web site has served well for the major associated events such as the conferences, announcements, and job postings. But it can do more, especially in strengthening the communication and networking among ICSA members. One approach is to use online news discussion forum for ICSA members to share tips, help each other, and to search for solutions to problems in archives that other members have discussed before. I strongly support the ideas proposed by our Executive Director in expanding ICSA's online services for members. Finally, I sincerely thank all of you for giving me the opportunity to contribute to ICSA and the continuing support for the ICSA activities.
Brief Biography of Candidates

CANDIDATES FOR BOARD OF DIRECTOR

LI, Hung-Ir


WEI, Greg Chung Guang


CHEN, Jiuhua


HE, Xuming


YANG, Zhen Hai


WENG, Chung-Sing Wayne

[PRESENT POSITION] Dr. Weng is Statistical Director at the Department of Medical & Scientific Affairs, Schering-Plough Corporation. [FORMER POSITIONS]

Brief Biography of Candidates

CANDIDATES FOR CHAIR OF BIOMETRICS SECTION

IVAN SHI-FUANG CHAN

SUE-JANE WANG

[PRESENT POSITION] Dr. Wang is currently a senior mathematician statistician in Division of Biometrics II, Office of Biostatistics, Office of Pharmacoeconomics and Outcomes Research, Center for Drug Evaluation and Research, Food and Drug Administration.

[FORMER POSITIONS] Her former positions included research/teaching associate in biostatistics of UCLA, research/teaching associate in biostatistics of USC, senior biostatistician at UC; member of Statistical Society of America; member and Session Co-Director of the Committee on Biometrics, University of California, and the FDA. She has also frequently served as referee for many statistical journals.

SPECIAL TOPIC - WEATHER

China's 20 Years of Climate Forecasting Progress

Zhai Guang

China Meteorological Administration

The Chinese nation has a long history of meteorological forecasting. Since 1950, China has made great progress in climate forecasting. In the past 20 years, China has developed a comprehensive and advanced climate forecasting system. The following is a brief overview of the development of climate forecasting in China.

Key Words: Climate forecasting, climate model

1. Introduction

China has a diverse climate with various types of weather patterns. The climate is characterized by high temperatures in the summer and low temperatures in the winter. The country is also subject to typhoons, floods, and droughts. Climate forecasting is crucial for disaster prevention and mitigation.

2. Methods and Applications

China has developed a comprehensive climate forecasting system that includes both numerical and statistical methods. The numerical methods include atmospheric models and climate models, while the statistical methods include regression analysis and machine learning algorithms. These methods are used to predict future weather patterns and assess climate change impacts.

3. Forecasting Tools

China uses advanced forecasting tools to improve the accuracy of climate predictions. These tools include high-performance computing systems, advanced data processing software, and remote sensing technologies. These tools enable the forecasting team to analyze large amounts of data and make accurate predictions.

4. Challenges

Climate forecasting faces numerous challenges, including data quality, model accuracy, and climate change. Despite these challenges, China has made significant progress in climate forecasting and continues to improve its systems and technologies.

5. Future Prospects

China is committed to advancing climate forecasting. The country is investing in research and development to enhance its forecasting capabilities. The future of climate forecasting looks promising, with ongoing efforts to improve accuracy, reliability, and accessibility.

References


Acknowledgments

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2. 判斷分析

廣東省氣候變異[19]用二階兩判判斷法處理地的預測。Fisher - Bayes 法以及逐步判別等雖然
在氣候預測上廣泛應用。判斷地可以。這些方法儘管判別為正態分隔時才用得
判斷判別對判別的複合及判別的判別地分隔判別應用本方法是可行的。且可用
判別判別的判別判別應用為判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判別判别
之間的語譯平方向高值（0.6）的臨界值。符號涵義則利用渉與正交點擺鑽和對應直線相等強度
之間的反相格面回覆關係。
6.2 大腦波頻譜
在連續功率頻譜中，自相關圖波和樣本值大小有關。1967年Barr提出了一種稱之為“大
腦”波頻譜的方式，具有解析度高、適用於短資料等優點。癲癇及精神障礙領域退化感的強
性和用相噪擾過早預測的確診，會產生等級。討論了震動序列的自相關頻譜分析，解圖譜
利用腦電圖儀記錄1950－1960年華北地區春季乾旱指數序列的顯著週期。
6.3 偶極型分析（CCA）
奇異分析（Singular Spectrum Analysis）是從時間序列的動態模式中發掘和驗證性質圖譜
所結合的一種統計技術。特別適合於大腦的非線性動態。上文所提及的感磁異型，Jia等
和Xia等利用CCA方法對發燒癲癇的頻率波型進行分析，發現發燒對癲癇的熱帶波型存在顯著
的預測性，發現20－22年的週期拉格，發燒時的熱帶波型存在明顯的8年，3－4年的週期拉格，發燒時的熱帶波型存在
12－14年的週期拉格。
6.4 小波分析
小波分析是從奇異波型分析方法發展起來的，並被認為是傅立葉分析方法的突破性進展。最新報
告和顯示
用小波變換研究了脈絡和脈衝領域的複雜性問題，並就其結果小波分析對幅資料
百年來氣候變化作出長期預測進行分析，預示變化等級，用小波變換分析農業資料的數據特性
變化，著重分析了中低頻頻率在小波徑跡圖中的分形特性，並根據分析結果對未來1－2年的低氣
候預測進行了預測。
7 時間序列模式
在氣象上用得最多的方式有自回歸模型（AR）、滑動平均模型（MA）、自回歸滑動平均模
型（ARMA）、_NAIMA模型，氣象模擬的時間序列數據是脈衝樣本化的上述
的時間序列數據是脈衝樣本化的，而時間序列分析中至脈衝樣本化（TAR）是一種脈衝樣本化
模型，它利用脈衝樣本化的內在脈衝樣本化系統，由於脈衝樣本化的控制，保留了脈衝樣本
化模擬的特有特性，可以方便地進行脈衝樣本化模擬，可以解釋脈衝樣本化的脈衝樣本化系統
等級。黃輝等利用目標函數全波形模擬模型

8 多層次擴展
1983年Efron提出建立在現代控制理論中“系統辨識”基礎上的時間變參數的
新的系統辨識方法－參數擴展技術，這種時間變參數的系統辨識方法在氣候預測及預報中取得了較不的效果
等級，不少學者在利用這種方法作這種方法的應用方面作了進一步的研究，在對氣候預測應用上
得到進一步的擴展。
9 均蓄態模型
1950－1960年華北地區春季乾旱指數序列和對應直線相等強度
之間的反相格面回覆關係，《 insanların doğası》

10 形態變態預期模型
“形態變態”理论，是新一代學者所提出的新形態理論。到目前為止，人们对天氣（氣候）
系統的變態現象、發展、消亡機制，子系統間的相互作用的瞭解尚不完全，不充分。限制了
動態預測方法在天氣（氣候）系統的深入研究。天氣氣候系統，由於其複雜性，是一個典型的大
規模的複雜的系統。訓練中對於天氣系統的觀測結果，根據天氣預報系統的天氣系統模型
的系統規模和天氣系統規模，其在氣象中的應用作了詳細的介紹，是統計升高等等根據的
模型的天氣系統的方法，作降峰期的中間預報。

參考文獻（略）

ICSA Bulletin
Bridging Studies

Implementation of Bridging Strategy in Taiwan

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Introduction

Recently, with the advance of human genome decoding and pharmacogenomics, issues on ethnic and population differences have taken the center stage in the new drug approval process. Since most of the new medicines were developed in western countries, the efficacy and safety of a drug was generally established based on Caucasian majority. Whether the foreign clinical data could be naïvely extrapolated to the population of a new region would be a major concern, especially in Asia. In March 1997, a consensus has been reached for ICH-ES (1). The guidelines address both the intrinsic and the extrinsic factors that are associated with drug characteristics, culture and environment; and provide a framework for evaluating the impact of ethnic factors upon the medicines’ effect. The principal objective of ES is to expedite the global development and availability of new medicines to patients without sacrificing the quality, safety and efficacy. While minimizing duplication of clinical studies, the guidelines also facilitate the use of bridging studies to allow extrapolation of foreign clinical data to a new region. Since the introduction of ICH-ES and the bridging concepts, awareness has increased among nations about the need for local clinical trials. Many Asian countries including Japan, Korea, and Taiwan, have formally announced the implementation of the bridging study requirement. Other Asian countries are also showing great interest in setting up a well-designed bridging study system.

In order to create a united Asian market under the harmonized regulatory system, Taiwan is leading and promoting the "APEC (Asian Pacific Economic Cooperation) Network of Pharmaceutical Regulatory Science - APEC Joint Research Project on Bridging Study". Two regional workshops were held in Taipei in 2000, and 2001. Scientific data related to ethnic factors were reviewed systematically in the meetings. With the help from CDE (Center for Drug Evaluation), the Department of Health has successfully developed a sponsor self-evaluation check-list, a decision-making tree, and consultation procedures (see CDE Website at http://www.cde.org.tw).

As well, the Department has planned educational workshops and set up a statistical working group. Requirement of a possible bridging study was formally announced on Dec, 12, 2000, giving a 2-year transition period (until Dec. 12, 2002) to phase out the current local registration trial requirement.

Evaluating the necessity of a bridging study

In general, Taiwan accepts all Asian data. A study by Lin et al. in 2001 (2) found that the so-called "Taiwanese", accounting for 91% of the total population in Taiwan, is comprised of Minnan and Hakka people who are closely related to the southern Han, and are clustered with other southern Asian populations in terms of HLA typing. Those who are the descendants of northern Han are separated from the southern Asian cluster, and form a cluster with the other northern Asian populations. As the Taiwanese regulatory authority acknowledges the trial data conducted in Taiwan regardless of the ethnic origin of the subjects, it will acknowledge all Asian data as well.

From the regulatory point of view, ethnic factor should not be defined completely by "Citizenship" or "Race". In the evaluation of ethnic differences, "Drug Characteristics" and "Indication" are the two fundamental elements to be considered. For example, some medicines are metabolized by enzymes with genetic polymorphism. If there is a higher percentage of poor metabolizers in Taiwanese patient population for a particular drug, adjustment of the claimed marketing dose may become necessary. Usually, hepatotoxicity is a major safety concern in bridging assessment. Due to the high prevalence rate (18%-20%) of HBsAg carriers in Taiwan, the need for more experiences with the usage of liver toxic agents in hepatitis B or C carriers may lead to the necessity of an additional bridging study. Difference in disease epidemiology and disease manifestations is another important issue. As illustrated in the case with female postmenopausal syndrome, Caucasian women usually present more vasomotor symptoms in contrast to Taiwanese women whom vasomotor symptoms are not predominant (3). Therefore, new agents whose efficacy was demonstrated by improved Kupperman Index score (which is weighted on vasomotor symptom domain) may not be accepted outright. Further investigations on Taiwanese postmenopausal women, using an index scale more suitable for this population (i.e., Greene Climacteric Scale) may be needed. Furthermore, medical practice between regions usually reflects one of the greatest variation and is the most difficult to harmonize. Differences in diagnostic criteria for some diseases, potential of drug abuse and possible drug-drug interactions are all essential considerations in evaluation for bridging studies.

In the past, little Asian clinical data were provided with the clinical data package used for new drug registration in Taiwan. Statisticians usually made no contribution in the bridging assessment since no information could be obtained from such limited data points. In some situations, PK profile obtained
Designing a bridging study

The acceptance of foreign clinical data will depend completely on its ability to be extrapolated to Taiwanese population. When this is in doubt, supplemental bridging data may be requested by the regulatory authority. In general, bridging study could be widely applicable to trials of any phase, including pharmacokinetic and pharmacodynamic studies, and phase III controlled clinical trials. However, a phase III controlled clinical trial is preferred because it is the most favorable study when there are uncertainties about dose, when there is limited experience with the drug class, or when there are safety concerns.

Ideally, a bridging phase III trial should have a study design identical to the foreign pivotal study. However, a full phase III clinical trial may not be practical considering small individual market in the local region. To remedy this and to accelerate the approval of a good medicine to be marketed in Taiwan, several compromising strategies are proposed. For example, we may allow the widely accepted surrogate endpoints to serve as primary efficacy endpoints, i.e., bone density in place of bone fracture in osteoporosis trials and objective tumor response rate in place of patient survival in cancer trials. Under some circumstances, the study period may be shortened clinically justifiable. Though a sample size computed to powerfully address similar efficacy and safety to those of pivotal studies is scientifically more sound, it is to our knowledge that the calculated sample size is often too large to be practical. Alternatively, a positive drug effect \( d_0 \) in Asian population is thought to be sufficient in sample size justification given that the effect of the original pivotal studies \( d_0 \) has been shown positive, and \( d_0 \) is within an acceptable range of \( d_0 \) (5). In terms of significance level and power used in computing required sample size, we consider protecting only the type I error. The one-sided alpha level could be relaxed with an upper bound of 10%. As for the power, we deem it the sponsor’s responsibility.

Conclusions

The new requirements for bridging study have ushered a new paradigm for regulatory approvals in Taiwan. Previous administrative formality such as the requirement of small-scale local registration trial for all drugs and free sale certificates will be gradually phased out. However, to draw a statistical inference with regard to bridging evidence by comparing two extremely unbalanced samples (i.e., size 20:1) of two patient populations from a single trial, or two separate studies is non-trivial. The statistical work on this field is still in a preliminary stage. We encourage all ICSA members to join us in settling these interesting and challenging issues.

Perhaps what is more important than the specifics of our statistical approach is that all pharmaceutical parties worldwide should work collaboratively in the process of new drug development. We would emphasize that “bridging study” is only a transitional strategy. We believe that with accumulated empirical experiences over time, bi-directional extrapolation (Asian data being extrapolated to European population and vice versa) for several classes of drugs will become a reality and, therefore, additional local clinical trials will not be needed.

With the implementation of ICH E5 accompanied by practice of good regulatory sciences, great opportunities exist for Taiwan to participate in the global R & D and to establish sound IND consultation process. These efforts will ultimately benefit the health of Taiwan populations.

References

Overview of Statistical Issues for Bridging Studies

TH Grasela, MR Piedmonte, L Phillips

In 1990, the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) [4] was initiated with the goal of harmonizing the requirements for discovery, development, and approval of new medicines across different geographic regions. Regulatory agencies from three regions: Europe, Japan, and the United States, collaborated with leading experts from the pharmaceutical industries in each region in this initiative. The primary objectives of the ICH were to provide guidelines that would avoid unnecessary repetition of costly and time-consuming clinical trials and thus facilitate and expedite, without sacrificing safety or quality, approval of new medicines in different global regions.

The publication of ICH-E5 [5] in 1998 provided guidelines for evaluating the impact of ethnic factors on the safety, efficacy, dose, and dose regimen of a drug under development and to identify those drugs whose characteristics make them more or less likely to be sensitive to differences in ethnic makeup. Ethnic factors include those that are intrinsic, such as genetic factors, race, weight, and other physiological characteristics, as well as those which are extrinsic, including environmental factors such as climate, pollution, and medical practice. Properties of a compound which predispose it to be less sensitive to ethnic factors include linear pharmacokinetics, a flat exposure-response curve for efficacy and safety at a given dose and regimen, a wide therapeutic dose range, minimal metabolism distributed among multiple pathways, high bioavailability, low potential for protein binding or interactions with other drugs or diet, and low potential for inappropriate use. Properties which would indicate that a compound is more likely to be ethnically sensitive include non-linear pharmacokinetics, metabolism through a single pathway, metabolism by enzymes known to exhibit genetic polymorphisms, a highly variable bioavailability between subjects, low bioavailability, a high likelihood of use with other medications, and a high likelihood of inappropriate use.

These guidelines provide loose criteria but do not provide clear scientific quantification of characteristics or thresholds of differences beyond which ethnic sensitivity would be assumed. A review of the literature in the Medline and Current Index to Statistics (CIS) databases shows that, although several authors have articulated many issues that need to be considered in global drug development, in general these expositions stop short of offering specific statistical methodologies. [3,6,11]

Thus, it is incumbent on the statistical community to collaborate with medical professionals to develop criteria for identifying the thresholds and statistical tests for establishing whether such thresholds have been crossed. The statistical community is also charged with developing appropriate designs for bridging studies and appropriate analysis methodologies for data from such studies.

Quantitative methods to be used for global drug development must address pharmacokinetic endpoints, pharmacodynamic outcomes of efficacy and safety, and the exposure-response relationship. These endpoints may be continuous, ordinal, dichotomous, or time-related and distributions of these endpoints may be normal, skewed, or bi-modal.

There are several considerations which will determine the appropriate direction for statisticians. First, the typical goal of bridging studies, as explicitly stated in ICH-E5, is to demonstrate that the properties of the drug are similar, rather than different, across global regions. Thus, with the goal of showing that the pharmacokinetics, efficacy, and safety of the drug are similar between global regions, tests of equivalence may be more appropriate than standard hypothesis tests. Within the equivalence framework of hypothesis testing, acceptance of the alternative hypothesis allows one to conclude that the regions are the same within a predefined amount (e.g., 20%). However, if the alternative hypothesis cannot be accepted, the resulting confidence interval can be used to place the comparator region on the scale of the previous safety, efficacy, and exposure findings in the reference region. Within the standard difference framework of hypothesis testing, rejection of the alternative hypothesis (regions are different) does not allow one to conclude that the regions are the same (the null hypothesis). Because these studies are powered to detect differences of a certain magnitude in this standard framework, this could result in an increased number of false-negative findings of small but important regional differences. Tests for bioequivalence of pharmacokinetic parameters are well developed and accepted. Therefore, a natural component to a global drug development program might be to conduct studies with pharmacokinetic sampling in multiple ICH regions and develop sample sizes to detect equivalence between pharmacokinetic parameters across regions. With the growing use of non-linear mixed effects modeling (NONMEM), the pharmacokinetic parameters could be obtained from Phase I studies in healthy volunteers with extensive sampling or a Phase II study in a representative patient population with sparse sampling. Further statistical methodologies are needed to address the issue of establishing equivalence between ICH regions with respect to efficacy and safety outcomes.

Ideally, domestic and foreign studies would be conducted simultaneously using a sampling strategy designed to obtain valid data for the estimation of pharmacokinetic parameters and for the assessment of efficacy and safety endpoints. For example, a parallel-group design stratified by region and by subgroups within region could be powered to simultaneously compare a new drug to a placebo both within and between geographic regions while allowing for unequal group sizes so that countries with economic or societal constraints could enroll fewer patients.

Such studies might be designed to assess the impact of regional differences in the pharmacokinetics of a drug and in toxicities as proposed by O’Neill. [8] O’Neill proposes modeling the hazard of adverse events as functions of time-dependent pharmacokinetic parameters such as cumulative AUC, along with other patient covariates that may be different with respect to region, in a model such as Cox’s proportional hazards model. [1] This approach appropriately accounts for the fact that adverse events
occur over a varying period of time and may be associated with exposure measures which also may vary over time. Patient characteristics in different ICH populations are thought of as covariates that take on different values for different types of patients, and the assumption is that patients in both regions have the same, albeit unknown and unspecified, underlying baseline risk of adverse events. If such an assumption is reasonable, then tests for interactions between exposure covariates and region-specific patient characteristics can be used to assess whether the exposure-toxicity relationship between patients in different regions is similar or different. For the simplest case, where toxicity can be defined as dichotomous (present or absent) and with an ethnic factor (present or absent) and a drug regimen (A or B), O’Neill proposes methodology to estimate the required sample size for detecting interactions between the ethnic factor and drug regimens in a pre-specified magnitude. Similar methodology would need to be developed to estimate the necessary sample size for assessing interactions between the time-dependent exposure measures and time-dependent toxicity outcomes as described above.

Often the manufacturer of a compound will conduct extensive studies in the region of origin only, and then, after these studies have proven the compound to be efficacious, seek global registration and marketing. It should be pointed out that there is a distinction between determining sample size for bridging studies that are conducted in a specific region after efficacy has already been shown in another region and those that are conducted concurrently in several geographic regions. In both cases, one would seek an appropriate sample size for the bridging study such that the study would be powered to detect equivalence using some predefined criteria, as is typically done in Phase I studies. However, it is necessary to recognize that, for tests of hypotheses comparing an historical group with one yet to be studied, the derived power function is random only through the region that has not yet been observed. Statistical methods for designing studies using historical controls have been developed for dichotomous [7] and survival time [2] endpoints utilizing the standard framework of hypothesis testing. However, these methodologies would need to be modified to detect equivalence rather than differences across regions, and new methods for continuous and ordinal outcomes would need to be developed.

An alternate methodology for designing a bridging study after substantial evidence of efficacy has been observed in several multi-center studies is proposed by Shih [9]. Shih argues that complete duplication of results in a new region is not essential provided one is reasonably confident that the results will be consistent with those already observed in other regions, and he also acknowledges that showing equivalence rather than difference is the ultimate goal of a bridging study. He proposes the idea of a “consistency trial” design based on Bayesian prediction whereby results from each previous study are used to construct a predictive probability distribution for specific results in the study for the new region. Criteria for concluding consistency are provided, along with sample size formula for normally distributed and binary outcomes. Such an approach is intuitive appealing and raises the point that the underlying goal of a bridging study is to show consistency, reproducibility, or equivalence in pharmacokinetics and pharmacodynamics of a drug between two regions.

In comparing pharmacokinetic parameters between patients in different regions, issues regarding skewness of distributions, different variabilities, and different measurement methods must be considered. The populations in different ICH regions may be so substantially different that statistical models which treat regional characteristics as different levels of a covariate may not be appropriate. Therefore, parametric assumptions may be more difficult to make in bridging studies and the use of nonparametric methods should be considered. One appropriate test for comparing pharmacokinetic parameters such as AUC between two populations is the Kolmogorov-Smirnov two-sample test [10]. However, much more complex differences in distributions can occur which would not lend themselves to this type of statistical test. For example, when drugs are metabolized by P-450 enzyme systems the underlying pharmacokinetic parameter distributions may have bimodalities, and the predominant mode may differ in different regions. Therefore, other statistical methods will need to be developed to handle such situations.

In summary, there are multiple tasks at hand for statisticians in the design and analysis of appropriate global drug development studies. This commentary identifies some of the issues and complexities that statisticians must consider. The existing methodologies proposed to date are a beginning, but much work remains.

REFERENCES
BRIDGING STUDIES: Is a bridge too far?

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I. Introduction

For marketing approval of a medicine, sponsors are required to provide substantial evidence of effectiveness and safety from adequate and well-controlled clinical trials. The U.S. Food and Drug Administration (FDA) recommends that at least two clinical studies (the so-called pivotal trials) in the same targeted patient population be performed to confirm the reproducibility of evidence on efficacy, safety, and dose response. However, after a medicine is approved by the original region (e.g., the United States of America), sponsors might seek registration of the product in a new region (e.g., Asian Pacific countries). The possible differences in ethnicity and clinical practice between the regions and their impacts on the safety, efficacy, dose and dosing regimen have limited the willingness of the regulatory authority in the new region to accept the clinical data generated in the original region. Consequently, the regulatory authority in the new region often requests the sponsors to repeat studies for obtaining all or much of the clinical data in the new region. This extensive duplication of clinical evaluation in the new region not only demands valuable development resources but also delays availability of the new medicine to needed patients in the new region. To resolve this dilemma, the International Conference on Harmonisation (ICH) has recently published a tripartite guidance entitled “Ethnic Factors in the Acceptability of Foreign Clinical Data” to address the above issues [1].

The objective of the guidance is to provide a framework for evaluation of the impact of ethnic factors on the efficacy and safety of a medicine at a particular dosage or dose regimen. In addition, it describes regulatory strategies of minimizing duplication for clinical data and requirement of bridging evidence for extrapolation of foreign clinical data to a new region. In general, the types of bridging studies required depend upon the ethnic sensitivity of the medicine, experience of the drug class, extrinsic ethnic factors and ethnic differences between the new and original regions. From ICH E5 guidance, the following table is a summary of types of bridging studies with respect to the above-mentioned factors:

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Region</th>
<th>Medical Practice</th>
<th>Drug Class</th>
<th>Clinical Experience</th>
<th>Bridging Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insensitive</td>
<td>–</td>
<td>Similar</td>
<td>–</td>
<td>–</td>
<td>No</td>
</tr>
<tr>
<td>Sensitive</td>
<td>Similar</td>
<td>–</td>
<td>–</td>
<td>Sufficient</td>
<td>No</td>
</tr>
<tr>
<td>Sensitive</td>
<td>Dissimilar</td>
<td>–</td>
<td>Similar</td>
<td>Familiar</td>
<td>PD</td>
</tr>
<tr>
<td>Choice of Dose</td>
<td>–</td>
<td>Different</td>
<td>Unfamiliar</td>
<td>–</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

From the above table, there are at least two fundamental issues in the ICH E5 guidance: (a) sensitivity of medicines to ethnic factors, necessity of a bridging study, and the nature and type of bridging studies, and (b) assessment of similarity based on bridging evidence. Because of complexity due to possible interaction among drug’s pharmacological class, indication, and demographic of patient population, the ICH E5 does not provide a precise and definitive criterion for evaluation of ethnic sensitivity. As a result, no probability statements can be made for the errors resulting from the decision-making on sensitivity to ethnic factors. Therefore, both regulatory authority in the new region and the sponsor do not have a criteria and a method for an objective and impartial evaluation of ethnic sensitivity and necessity of a bridging study.

On the other hand, there are thousands of medicines that were approved for various indications for different patient populations by various regulatory authorities in different geographic regions, e.g. the U.S. Drug Master File. Sufficient pre-approval and post-marketing experience on the above-mentioned properties for ethnic sensitivities and impact of intrinsic and extrinsic factors on efficacy, safety, dosage, and dose regimen have been accumulated for these medicines. An instrument can be developed for three domains. The first domain includes the basic properties of the compound mentioned above, The second domain consists of intrinsic factors mentioned in Appendix A of the ICH E5 guidance. Domain 3 is constituted of the extrinsic ethnic factors mentioned in Appendix A of the ICH E5 guidance. Within each domain, a scoring scheme for each property or factors is designed to represent the degree of impact on efficacy, safety, dose and dose regimen. A possible scheme is a 5-point system, 1 (no), 2 (mild), 3 (moderate), 4 (strong), and 5 (complete). Then an algorithm can be formulated to provide a summary index for an overall assessment of impact of the medicine on efficacy, safety, dosage, and dose regimen. These thousand compounds can be divided into two sets: training set and validation set. Based on the summary indices computed from the medicine in the training set, a threshold can be determined to classify these medicines into the group with no need of bridg-
ing studies and the group that bridging studies are necessary. Based on validation set, the probability of classification error can then be estimated. Within the group with the necessity for bridging studies, further cutoff points can be estimated for different types of bridging studies. When a new medicine is applied for registration in the new region, regulatory authority in the new region and sponsor can calculate this summary index to decide whether a bridging study is needed and what type of the bridging study is warranted. However, the above-mentioned task requires a joint and collaborate effort from clinicians, pharmacologists, pharmacoepidemiologists, medical informatics, and behavior scientists.

III. Assessment of Similarity Based on Bridging Evidence

According to the ICH E5 guidance, a bridging data package consists of (a) selected information from the Complete Clinical Data Package (CCDP) that is relevant to the population of the new region, and (b) if needed, a bridging study to extrapolate the foreign efficacy and/or safety data to the new region. In other words, bridging evidence is actually provided either in the CCDP generated during clinical drug development program for submission to the original region or in a bridging study conducted in the new region after the pharmaceutical product is approved in the original region. When the bridging evidence provided in the CCDP cannot allow extrapolation of foreign clinical data to a new region, then a bridging study should be conducted in the new region to generate a limited amount of clinical data to bridge the clinical data between the two regions.

Although the ICH E5 guidance clearly states that assessment of the ability of extrapolation of the foreign data rely on the similarity of dose response, efficacy, and safety between the new and original regions, either with or without dose adjustment, it does not provide a precise definition or criteria for evaluation of similarity. A direct interpretation of the ICH E5 guidance on similarity requires performing a between-region (study) analysis to evaluate the treatment-by-region interaction. It is then very clear that the sample size required for the test based on the treatment-by-region interaction will be much larger than that for detection of the treatment effect alone [2]. This statement is true for all types of studies and for all types of endpoints. On the other hand, one only wants to verify whether the evidence of efficacy or safety or PK/PD properties observed in the original region can be reproduced in the new region. In this context, for example, a statistical significance based on a particular endpoint can be also obtained from the bridging study conducted in new region if it had been observed in the original region. However, an equal or even larger sample size is required to reproduce a similar statistical significance for detection of treatment effect in the new region [3-6]. Therefore, these arguments indicate a fundamental conflict between the evaluation of similarity and the objective of minimizing duplication of clinical data in the ICH E5 guidance.

Consequently, Bayesian methods have been suggested to synthesize the data from both the bridging study and the original region to resolve this conflict [7,8]. However, some difficulties also arise using the Bayesian method. First, a medicine was approved in the original region due to its substantial evidence of efficacy and safety based on a sufficiently large sample size. The result of the bridging studies using empirical Bayes approach will be overwhelmingly dominated by the results of the original region due to an imbalance of sample sizes between the regions. In other words, it is very difficult, if not impossible, to reverse the results observed in the original region even the result of the bridging study is completely opposite. In addition, the Bayesian method for evaluation of probability for error of decision-making on similarity is still needed to work out. This error probability is extremely crucial for the regulatory authority in the new region to approve a medicine in their jurisdiction.

IV. Summary

The ICH E5 guidance provides a rationale for assessment of ethnic factors in the acceptability of foreign data for regulatory strategies of minimizing duplication of clinical data and it also describes and requirement of bridging evidence for extrapolation of foreign clinical data to a new region. It, however, is too premature to develop statistical methods for regulatory implementation unless the scientific and clear criteria (a) for evaluation of sensitivity of medicines to ethnic factors, (b) for assessment of necessity of a bridging study, (c) for determination the nature and type of bridging studies, and (d) for assessment of similarity based on bridging evidence are defined in the ICH E5 guidance.

References:

Some Current Statistical Issues with Bridging

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The International Conference on Harmonisation (ICH) E5 guideline: “Ethnic Factors in the Acceptability of Foreign Clinical Data”1 introduces the concepts “bridging” and “bridging studies” and provides broad guidance on the process known as “bridging.” ICH-E5 defines a bridging study as “a study performed in the new region to provide pharmacodynamic or clinical data on efficacy, safety, dosage and dose regimen in the new region that will allow extrapolation of the foreign clinical data to the population in the new region”. Simply put, the bridging process involves the extrapolation of clinical data generated from a foreign region (e.g., the West) to a new region (e.g., Japan) in order to obtain regulatory approval in the new region. Usually, the results of clinical trials conducted in the foreign region are known prior to conducting any clinical trials in the new region. The purpose of the bridging study is to generate enough data in the new region to demonstrate that extrapolation, or bridging, to the foreign region is possible. This will involve demonstrating that any differences in ethnic factors between the foreign and new regions have not altered the efficacy or safety of the drug in the new region. One of the advantages of the bridging process is that it negates the need for a separate clinical program in the new region and therefore avoids the need for unnecessary repetition of studies in the new region.

ICH-E5 states that if data generated from the bridging study shows that dose response, efficacy and safety in the new region are “similar” to the foreign region, the study may be readily interpreted as capable of bridging the foreign data. Although the ICH-E5 document is a major step forward, it does not contain guidance on the definition of “similarity”. Subsequent to the issuance of ICH-E5, the then Ministry of Health and Welfare in Japan (now encompassed within the Japanese Ministry of Health, Labour and Welfare) produced a Q & A paper2, which states: “it is impossible to suggest concrete standards to judge whether cited features of a drug are ‘similar’ or ‘not greatly different’ across populations”. It also mentions that “neither statistical ‘equivalence’ nor strict identicalness is requisite”.

If this is the case, then, what are the criteria for successful bridging? Since bridging is a multi-faceted issue, not just a statistical one, there is no single, straightforward answer to this question. The final judgement necessarily depends on a number of important considerations; political, ethical, philosophical and clinical. Nevertheless, the application of appropriate statistical methods can make an important contribution to the bridging process, and the area of bridging is certainly rich with challenges for the statistician. This article discusses some of the statistical issues that arise with bridging, but is by no means a fully comprehensive account.

ICH-E5 recommends that a fixed dose, randomised dose response study should be the first choice for a bridging study. Information on dose response often plays an important part in extrapolability. It is not necessary to include an active control in the bridging study. ICH-E5 states that it is inappropriate to provide guidance on the sample size of the bridging study in that document, as this necessarily depends on the disease area and choice of endpoints. The simplest, and perhaps the most appropriate way to calculate the sample size for the bridging study, is on the proposed analysis of the bridging study itself (e.g., a trend test for dose response, or an expected difference from placebo). An alternative method of sample sizing for the bridging study is to base the calculation on a statistical analysis that will subsequently be used to demonstrate extrapolability of the foreign data. This approach, however, is likely to lead to a prohibitively large bridging study.

Once the bridging study has been designed and analysed, how do we then demonstrate extrapolability? Some statisticians have chosen to view the bridging problem in much the same way as they would view an equivalence or non-inferiority trial. Using this approach, the aim is to show that some appropriate measure of efficacy or safety in the new region (such as the treatment effect or slope of the dose response curve) and the same quantity in the foreign region, differ by no more than some positive amount, delta. Stating the problem in this way does not bring us any closer to a definition of similarity; it merely restates the same question in mathematical terms. The unanswered question: “what do we mean by similarity?” is replaced by another unanswered question: “what should we choose for delta?”. Just as in equivalence and non-inferiority trials, the choice of delta would be a source of extensive debate, and would be different for different disease areas.

Another method of tackling the bridging problem is to fit a single statistical model to the combined data from the new and foreign regions, and test for the statistical significance of the treatment by region interaction (using appropriate measures of efficacy or safety as the outcome variables). This author considers that this approach is flawed in two ways. Firstly, although the detection of a treatment by region interaction means that the treatment effect is different between the two regions, it does not mean that the magnitude of the difference is of any clinical relevance. Secondly, failure to detect a treatment by region interaction, even in an adequately sized analysis, does not mean that there are no differences between the regions. As in all hypothesis tests, failure to reject the null hypothesis does not mean it has been proved to be true.

Rather than concentrating on the statistical significance of the treatment by region interaction term, an alternative approach would be to explore the nature and magnitude of this interaction using more informal methods, such as simple plots of the data, by region, with confidence intervals. Alternatively, or in addition to this, the treatment by region interaction term could still be fitted in a statistical model, but used to generate separate dose response slopes for different regions from the
same model. The standard errors for the estimated slopes can also be generated from the statistical model, and used to calculate confidence limits for the slopes. Covariates that may affect the estimates of the slopes may also be included in the statistical model. The assessment of similarity is then made from a visual inspection of the slopes. This judgement is made from a clinical point of view, but appropriate statistical methods have been used to (a) estimate the slopes of the dose response curves for each region, (b) provide appropriate measures of the variability in the estimates of the slopes, and (c) adjust the estimates of the slopes for any important covariates.

One popular approach to bridging between regions is to compare the results of a single bridging study in the new region with a single study of the same design from the foreign region. Usually, however, there is more than one study to choose from in the foreign region, and many of these studies could potentially contribute to the bridging analysis. One drawback of the "one-to-one" approach is that it can be difficult to provide a convincing justification for the choice of study from the foreign region if that choice is made after the results of the bridging study in the new region are known. One can easily be accused of choosing the foreign study with results that are "most similar" to the results from the bridging study in the new region. It may be preferable to identify which study from the foreign region will be used for bridging prior to knowing the results from the bridging study in the new region. But this may be a very difficult choice to make.

An alternative approach is to identify a set of studies in the foreign region that is representative of the overall clinical experience in the foreign region. That is, the studies should have a common set of endpoints, common design aspects, and include subjects from broadly the same population. The observed mean values of measured outcomes, or response rates, when calculated for the same endpoint will vary from study to study due to natural variation. This should not cause an issue for bridging, as the "similarity" of the results from the bridging study would then be viewed in the context of the variability already seen between studies in the foreign region. The study-to-study variation could be modelled appropriately by fitting a study term as a random effect in a statistical model. There is also potential for the data from the foreign region and the data from the new region to be incorporated into a Bayesian model.

It is likely that at some point in the near future, bridging will be superseded by the emergence of global clinical trials (i.e., single trials that simultaneously recruit subjects from the United States, Europe, Japan and other countries). This author believes that these multi-region trials present much the same statistical issues (and controversies) as we currently encounter with multi-centre trials. We should approach the analysis of multi-region trials in much the same way as we currently approach multi-centre trials. Conventional wisdom from multi-centre trials would suggest that we should power a multi-region study to show an overall treatment effect across the regions and then explore the presence of heterogeneity of the treatment effects between the different regions. Once again, a treatment by region interaction test may not be the best way to explore these differences, but appropriate plots and summary statistics (with associated measures of variability) may be more useful and informative. The treatment effect used in any sample size calculation would be the treatment effect we expect to see in the study as a whole, and the by-region results would be examined to see if there are any departures from the overall finding.

There may be a tendency, however, for some regulatory authorities to request a subgroup analysis in their region alone. This then leads to special consideration of the proportion of subjects that must be recruited from a specific region in the study, so that meaningful subgroup analyses can be conducted in that region. If subgroup analyses are to be carried out, the type I error rate should be appropriately controlled, otherwise statistical significance could be seen in one of the regions just by chance. The statistical challenges involved in designing and analysing global clinical trials, which meet the requirements of different regulatory authorities throughout the world, are likely to remain with us for many years to come.

References


Bridging clinical studies: many questions but few answers

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The concept of bridging studies was introduced in the ICH E5 document to facilitate the registration of pharmaceutical products among ICH regions. Clearly given in the document, a bridging study is defined as a study performed in the new region to provide pharmacodynamic or clinical data on efficacy, safety, dosage, and dose regimen in the new region that will allow extrapolation of the foreign clinical data package to the population in the new region. The similar concept can be stipulated in other contexts, such as, what data are needed to approve a drug for use in pediatrics given that the drug has been used for adult patients.

The first gigantic step is to decide whether a bridging clinical trial is needed for registration of a pharmaceutical product in a new region. The decision will involve a lot of knowledge, such as, the relationship between the pharmacodynamic response and the clinical outcome, interactions between these responses and covariates (e.g., ethnic factor, drug administration, medical practice) that are suspected to have influence on drug effect. The problem of surrogate markers needs to be of concern here and generally cannot be trivialized. On the other hand, if a drug has been approved to save lives in some disease patients in the foreign region, then how much of additional data are needed for the same indication to be granted in the new region? Extremely careful deliberation is very much needed because it has tremendous public health implication in the new region, knowing that direct explanatory power of pharmacodynamic data is limited.

When a bridging clinical trial is required, the expectation of little difference in drug effect between the new region and the foreign region is undoubtedly challenged. It is, however, not clear what the objectives of the bridging clinical study are. At the minimum, the bridging clinical study must conclude that a dose or dosage regimen of the drug chosen to be marketed in the new region is effective (i.e., beats placebo) and safe. Another objective is, as many argue, to show that this dose has similar therapeutic effectiveness as the dose approved for marketing in the foreign region. However, it is not clear why the latter objective is relevant for registration. This subject has already been discussed in literature, such as, Shao and Chow (2002), Liu, Hsu, and Chen (2001), Liu (2002), Ware (2001).

The bridging clinical trial has sample size limitation. The ICH E5 document describes the regulatory strategies that minimize duplication of clinical data in facilitating acceptance of foreign clinical data in the new region. To explore the feasibility of a bridging clinical trial, let \( d_1 \) be the dose to be marketed in the new region and \( d_1 \) the approved dose in the foreign region, where \( d_1 \) may or may not be the same as \( d_1 \). Let \( \theta_1 \), be the corresponding mean effect (i.e., \( 1 \)). The foreign region has established the effect \( \theta_1 \), with the estimate \( \hat{\theta}_1 \) and relevant 1-sided p-value \( p_1 < 0.025 \). To test the efficacy of \( d_1 \) in the new region, the distribution of the \( p \)-value \( p_2 \) associated with \( \theta_1 \) based on Hung et al (1997) is \( \Pr \{ P_2 < p_1 \mid \theta_1 = L \} = \Phi \left( -\Phi^{-1}(1-p_1) + M/\sqrt{\lambda} \right) \), where \( \Phi \) is the distribution of the standard normal distribution, \( M \) is the sample size of the new region, and \( \lambda \) is a constant. Assuming equal variability of the response between the regions, given \( t_1 \), the sample size \( M \) required for detecting \( \theta_1 = 4\theta_1 \) at significance level (1 - power) 1 - \( \beta \) is

\[
M = \left\lceil \frac{(1 - \alpha)(2\Phi^{-1}(1-\beta))^2}{(1 - \beta)^2} \Phi^{-1}(1-p_1)^2 \right\rceil
\]

Thus, for \( \alpha = 0.025 \) and \( \beta = 0.20 \), if \( p_1 = 0.025 \), then \( M \) will be 2.64M for detecting \( \theta_1 = 1 \). If \( p_1 = 0.001 \), then \( M \) will be 0.82M. If \( \theta_1 \) have variability, then the sample size \( M \) will be even more demanding. Shao and Chow (2002) made similar arguments. In the context of showing similarity in drug effect between the two regions, it can easily be imagined that the sample size will need to be much greater (Liu, Hsu, and Chen (2001), Liu (2002)). Recognition of the sample size limitation of the bridging clinical study prompts several intriguing ideas for designing a bridging clinical trial. Examples are: Chow (2001) created a sensitivity index to determine the chance of reproducibility and generalizability based on the observed clinical data for determining when a bridging clinical trial with a certain sample size can be recommended, Shih (2001) stipulated the concept of showing 'consistency' by use of the predictive probability as a measure of the plausibility of the results of the new region given the known results of the foreign data, and Wang and Kung (2001) considered raising alpha error to exchange for sample size feasibility.

We should be reminded of the fact that in designing a bridging clinical trial there has been substantial to rich experiences with the drug from the foreign data. Perhaps the dose response data are not sufficient for extrapolation. But at least, there is plenty of experience with the marketed dose of the drug. Can the foreign data help to refine the clinical and statistical hypothesis for bridging clinical trial? For instance, when testing hypothesis of similarity, can we consider only the type I error rate within the new region. That is, the uncertainty in the estimate of the drug effect from the foreign region is only used for the purpose of designing the bridging study, not incorporated in the calculation of type I error for the new region. Another question is, should one-sided hypothesis be sufficient? Flexibility must be kept in mind in each application at hand.

In this era, drug development has become global. Thus, at the planning stage of drug development, the strategy of global multi-national clinical trial is appealing. Each region becomes a specific subgroup. Internal validity can be achieved. This strategy will demand consistency in clinical trial standards and regulatory standards among the regions. However, if regional differences in drug effect are suspected, then the percent representation of each region will become a contentious issue. Nonetheless, the global average of \( \theta_1 \) will better reflect the drug effect over the multiple regions. Can the global clinical trial strategy solve the problem of bridging clinical trial? It is not likely. We have long experienced the difficulty in interpretation of subgroup results when the subgroup analysis shows apparent heterogeneity among subgroups. In fact, the problem
Some Upcoming Statistical Meetings

Third International Conference on Multiple Comparisons Procedures
August 04–07, 2002, Bethesda, Maryland, USA

Beyond the Formula Statistics Conference
August 08–09, Rochester, New York, USA

2002 Joint Statistical Meetings
August 11–15, 2002, New York, USA

The 4th Survey Research Methodology and Its Applications Conference.

Statistical Concepts for Non-Statisticians
September 09–10, 2002, San Diego, California, USA

Symposium on Biomedical Technology Development (visit our website for details)
September 28–29, 2002, Rockville, MD, USA

Applied Statistics Conference at NC State
October 30–01, 2002, Raleigh, North Carolina, USA

The Second Annual Emerging Information Technology Conference
— Nanotechnology, MEMS, Systems on Chip, and Bioinformatics Workshops
November 01–02, 2002, University of Princeton, Princeton, New Jersey, USA

BAMMCONF: Bayesian Applications and Methods in Marketing Conference
November 13–16, 2002, Columbus, Ohio, USA

Eleventh Annual Meeting of the International Genetic Epidemiology Society
November 15–16, 2002, New Orleans, Louisiana, USA

10th Merck-Temple Conference
November 22–22, 2002, Philadelphia, Pennsylvania, USA

International Conf. on Applied Statistics, Actuarial Science, Financial Mathematics
December 17–19, 2002, Hong Kong, International China

ICSA 2003 Applied Statistics Symposium (visit our website for details)
June 22–24, 2003, University of San Diego, San Diego, California, USA
INTERNATIONAL CHINESE STATISTICAL ASSOCIATION

Events at 2002 Joint Statistics Meeting at New York

Caucus of Women in Statistics (ICSA Cosponsored)
Time: 6:00 PM–7:30 PM, Sunday, August 11, 2002
Place: Mercury Rotunda at Hilton Hotel

Board of Directors Meeting
Time: 7:30 PM–10:30 PM, Sunday, August 11, 2002
Place: Liberty Suite 3 at Sheraton Hotel

Statistica Sinica Board of Directors Meeting
Time: 10:30 AM–12:00 PM, Tuesday, August 13, 2002
Place: Liberty Suite 5 at Sheraton Hotel

Statistica Sinica Invited Papers Session
Time: 8:30 AM–10:20 AM, Wednesday, August 14, 2002
Place: Royal Ballroom B at Sheraton Hotel

Membership Meeting
Time: 6:00 PM–7:30 PM, Wednesday, August 14, 2002
Place: Concourse B at Hilton Hotel

Year 2002 Banquet
Time: 7:30 PM, Wednesday, August 14, 2002
(Right after the Membership Meeting)
Place: The Peking Park Restaurant at 100 Park Ave., NY, NY 10017
Entrance at 40th Street, Between Park & Madison Ave.
After Banquet Entertainment: Karaoke (please volunteer?)
Cost: $30/person

Please register and pick up Banquet ticket at the ICSA Booth at JSM2002.
To help for head count, please register before Wednesday, August 14

Information and Banquet Registration:
Wei-Yann Tsai, wtsi@biostat.columbia.edu tel # 212-305-9408

ICSA 2003 APPLIED STATISTICS SYMPOSIUM
JUNE 22-24, 2003
San Diego, California
http://www.icsa.org

Theme: Statistics in Bio-tech Research and Computing Intensive Methodologies

DATE: June 22 to 24, 2003. Short courses on Sunday, June 22, and technical sessions on Monday, June 23 and Tuesday, June 24.

LOCATION: University of San Diego. For local attractions, please visit the hotel website http://www.sandiego.org/whattodo.asp

ACCOMMODATIONS: The room rates of lodging at University of San Diego range from $50.00/night /person without meal to approximate $100.00/night/person with meals.

CALL FOR PAPERS: The program committee invites you to submit statistical papers to be considered for presentation at the symposium. Abstracts are due March 31, 2003. Please submit abstracts to: Professor Gang Li, University of California at Los Angeles, email address: gangli@sunlab.ph.ucla.edu. The abstract should include the name, affiliation, mailing address, telephone number, fax number, and e-mail address of the author, and should not exceed 200 words. A template for the abstract can be downloaded from the ICSA website at http://www.icsa.org

ICSA STUDENT AWARDS AND TRAVEL FELLOWSHIPS: The deadline is February 28, 2003 (see a separate page in this issue for detailed information). For further questions, please contact Professor Kung Jong Lui, San Diego State University, kjl@rohan.sdsu.edu

EXECUTIVE COMMITTEE
Co-chair of the symposium: Nancy Lo (Nancy.Lo@NOAA.Gov) and Gang Li
Secretary: Alice Chu
Treasurer: Kathy Chi-Burris

Program Committee:
Gang Li (co-chair), Larry Shen (co-chair), Naihua Duan, Keh Shin Lii, Ying Lu, Kung Jong Lui, Edward Pun, Weng-Kee Wong, Eric Yan, Nancy Lo, and Joey C. D. Lin

Logistic Committee:
Nancy Lo (Chair), Alice Chu, Kathy Chi-Burris, William Yuan, David Shen, George Yu, John Lee, Thomas Lin, Kung Jong Lui, Xun Lin, Christina Show, Eric Yan, Joey C. D. Lin, Jenny Han and Edward Pong.
PRELIMINARY PROGRAM
ICSA 2003 APPLIED STATISTICS SYMPOSIUM

• Keynote Speakers (June 23-24, 2003):
  Bradley Efron, Professor of Statistics and Biostatistics, Stanford University, President-Elect, ASA.
  http://www-stat.stanford.edu/people/faculty/efron.html
  George Tiao, W. Allen Wallis Professor of Econometrics and Statistics, University of Chicago,
  http://gsb.uchicago.edu/fac/george.tiao

• Plenary Sessions (June 23-24, 2003):
  Recent developments in nonparametric inferences with applications to biomedical studies and financial modeling, by Jianqing Fan
  PK-PD modeling in drug research and development, by Tze Leung Lai

• Banquet Speaker: Arlene S. Ash, Boston University. (Lucky Star Chinese Sea Food Restaurant.)

• Short Courses (Sunday, June 22, 2003):

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<tr>
<th>Topic</th>
<th>Instructor</th>
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<tbody>
<tr>
<td>1</td>
<td>Practical Guidance of Generalized Linear Mixed Models</td>
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<td>2</td>
<td>Tutorial on Statistical Bioinformatics</td>
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<tr>
<td>3</td>
<td>Cancer Trials for Practitioners - Experimental Design, Efficacy Analysis, and Economic Implications</td>
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<tr>
<td>4</td>
<td>Bootstrap Methods: A Guide for Practitioners</td>
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<td>5</td>
<td>Active Controlled Clinical Trials</td>
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<td>6</td>
<td>Robust Parameter Design for Product/Process Improvement</td>
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Invited Sessions (June 23-24, 2003, not complete):

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<tr>
<th>Topic</th>
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<tbody>
<tr>
<td>1</td>
<td>Statistical Applications in Business Research</td>
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<td>Issues of Active Controlled Clinical</td>
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<td>3</td>
<td>Statistics in Risk Management</td>
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<td>4</td>
<td>Current Methodologies in Pharmaceutical Statistics</td>
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<td>5</td>
<td>Assessment of Measurement Agreement</td>
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<td>6</td>
<td>Recent Advances in Survival Analysis</td>
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<td>7</td>
<td>Data Mining in Chemistry and Chinese Medicine</td>
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<td>8</td>
<td>New Development in Medical Diagnostic and Screening Tests</td>
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<td>9</td>
<td>Statistical Methods for AIDS Clinical Research</td>
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<td>10</td>
<td>Design of Experiments</td>
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<td>11</td>
<td>Design and Analysis of Dose Response Studies</td>
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<td>12</td>
<td>Statistical Applications in Accounting, Economics and Finance</td>
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<td>13</td>
<td>Empirical Likelihood and Its Applications</td>
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<td>14</td>
<td>Computing Intensive Methodologies in Bayesian Statistics</td>
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<td>15</td>
<td>Functional Data Analysis</td>
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<td>16</td>
<td>New Development in Quality Improvements</td>
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<td>17</td>
<td>Statistical Methods for the Analysis of DNA and Tissue Microarray Data</td>
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<td>18</td>
<td>Markov Chain Monte Carlo and Its Applications</td>
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<td>19</td>
<td>Aspects of Clinical Trials</td>
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<tr>
<td>20</td>
<td>Bioengineering and Statistics</td>
</tr>
<tr>
<td>21</td>
<td>Intensive computing in genetic application</td>
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</table>
Student Award Winners

From: Weichung Joe Shih
Chair of the student awards and travel fellowship committee

TO: ICSA President, Executive Director, and Symposium Program Chair

Five papers have been submitted for the 2002 ICSA Student Awards and Travel Fellowships program by the deadline of Feb 28, 2002. The Student Award Committee (W. J. Shih of Univ. of Medicine and Dentistry of New Jersey, Con-Hui Zhang of Rutgers University and Zhiliang Yin of Columbia University) has selected the following three papers according to the program guidelines.

These students and paper titles are (by the order of ranking):

1. Zhengjun Zhang, University of North Carolina, Chapel Hill, “Modeling financial time series data as moving maxima processes”. (With Richard L. Smith)

2. Jun M. Liu, University of Illinois at Chicago, “Modelling hourly electricity loads using a semi-parametric time series approach”. (With Rong Chen and Lou-Mu Liu)

3. Yi-Chuan Zhao, Florida State University, “Goodness-of-fit test for proportional hazards assumption via empirical likelihood”. (With Ian W. McKeague)

Each of the above three students will receive a certificate, $400, and tuition for the short courses of their choice at the Symposium.

Registration Form

Biomedical Technology Development

September 28-29, 2002
University of Maryland, Shady Grove Campus, Building 1, Auditorium
9640 Gudelsky Drive, Rockville, MD 20856

<table>
<thead>
<tr>
<th>Name</th>
<th>(Chinese)</th>
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<tr>
<th>Registration fee (include 09/28 lunch)</th>
<th>Before 9/10/02 (per person)</th>
<th>After Sept. 10 (per person)</th>
<th>Vegetarian (Yes or No)</th>
<th>Num. of person</th>
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Total amount

1. Please mail the registration form and a check payable to “SCBA” by 09/10/2002 (no cash, please):
   SCBA, c/o Ms. Pat Oldewurtel
   Johns Hopkins Asthma and Allergy Center, Room #1A-62
   5501 Hopkins Bayview Circle, Baltimore, MD 21224
   Tel: 410-550-2001 Fax: 410-550-2527

2. Registration fee includes program book, lunch (9/28), coffee, soft drink.

3. Please call (8:30-17:00):
   Shau-Ku Huang (410-550-2006); Sue-Jane Wang (301-983-3591)
   Cathy Wu (202-887-2121); Shih-Mei Huang (301-827-7688)
   Jih Shao (202-895-1931).
### Symposium on Biomedical Technology Development
**September 28-29, 2002**
University System of Maryland, the Shady Grove Center
9640 Gudelsky Drive, Building I-134, Auditorium 305
Rockville, MD 20850

#### 會議行程 (Program)

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<td><strong>Plenary session</strong></td>
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<tr>
<td>08:30 – 08:35</td>
<td>Opening Remarks</td>
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<tr>
<td>Dr. Yaw-Nan Chen 陳耀南, TECRO-Science Division - to be confirmed</td>
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<tr>
<td>08:35 – 09:40</td>
<td>Keynote Speech (Dr. Yaw-Nan Chen to confirm)</td>
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<tr>
<td>09:40 – 10:00</td>
<td>Morning Break</td>
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<tr>
<td><strong>Session 1</strong></td>
<td>Emerging Biotechnology - Vaccine Development</td>
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<tr>
<td>Don Chen 陳東健, Ph.D., SynAm</td>
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<tr>
<td>Keith Chan 陳桂愷, Ph.D., GloboMax</td>
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<td>10:00 - 12:00</td>
<td>Vaccine</td>
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<tr>
<td>Shau-Ku Huang 黃鸝谷, Ph.D., Johns Hopkins</td>
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<td>Vaccine Industry - OEM or QPM for innovation</td>
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<td>Wenli Lin 林文理, Ph.D. ADimmune</td>
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<td>The Need of Vaccine Development in Taiwan</td>
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<td>Shiing-Jer Twu 汪登哲 M.D., Ph.D., Director General, CDC, Taiwan</td>
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<tr>
<td>Panel Discussion (Clinical and Regulatory)</td>
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<tr>
<td>Shousun Sze, 陳學森 Ph.D. NICHD/NIH</td>
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<tr>
<td>Kimi Feng-Ying C. Lin, 邱蝮英 M.D. NICHD/NIH</td>
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<tr>
<td>Chi-Jen Lee, 李啓仁 D.Sc. CBER/FDA.</td>
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<tr>
<td>12:00 noon-1:00 pm</td>
<td>Lunch (catereria)</td>
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<td><strong>Session 2:</strong></td>
<td>Current Biotech Investment in Taiwan and Europe</td>
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<tr>
<td>Chuang C. Mike Chiueh 陳壯淵, Ph.D., NIH</td>
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<tr>
<td>Leon Tseng 鄭良福, Ph.D., Medical College, Wisconsin</td>
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| 13:00 - 15:00 | US Patent developed by Academia: antiseptic Shock or iNOS Suppresor |
| M.J. Su 蘇明成, Ph.D., Pharmacology Institute, National Taiwan University, Medical School |
| US Patent developed by Industry: Anti-enterovirus Agents from Algae |
| C. Chun Chiueh 陳壯淵, C.E.O., FarEast Algae |
| Clinical Trials: Conjugated Blood Clot Busters |
| P.-W. Hong 洪博文, M.D. / S.S. Yang 楊健旭, GlobalGene |
| Emerging European Biotech Company: From Bench-Top Idea – Patents – Clinical Trials of New NO Drugs |
| Pico Del Soldato, Ph.D. / Jean-Luc Burgaud, Ph.D., Nicox SA |
| 15:00 - 15:30 | Afternoon Break |
| **Session 3** | Biochip Technology and Data Mining |
| Sue-Jane Wang 王淑貞, Ph.D., CDER/FDA |
| Cathy Wu 吳慧華, Ph.D., Georgetown University |
| 15:30 - 17:30 | “Seriation algorithms for identifying smooth temporal pattern and global clustering structure in cDNA gene expression data” |
| Chun-Houh Chen 陳明厚, Ph.D., Institute of Statistical Science, Academia Sinica, Taipei, Taiwan |
| “Current status of biochip technology development, where is it headed, and its commercialization potential” |
| Chung-Cheng Liu 留長正, Ph.D., Industrial Technology Research Institute, Hsin Chu, Taiwan |
| “Bioinformatics and Functional Genomics/Proteomics” |
| Cathy H. Wu 吳慧華, Ph.D., Georgetown University |
| 19:00 – 22:00 | Dinner Banquet (New Fortune restaurant 新財神, Gaithersburg, MD) |
| Dinner speaker |
| World renowned forensic criminal scientist – Henry Lee 李昌鈺博士, Ph.D. |

<table>
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<tr>
<th>Day 2</th>
<th>September 29 (Sunday), 2002</th>
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<tr>
<td><strong>Session 4:</strong></td>
<td>Pharmacogenetics, pharmacogenomics, and biomarkers: When is personalized medicine possible?</td>
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<tr>
<td>Shiew-Mei Huang 顏秀美, Ph.D., CDER/FDA</td>
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<tr>
<td>Shau-Ku Huang 黃鸝谷, Ph.D., Johns Hopkins University</td>
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If I Could Do It All Over Again

T. Timothy Chen
Southwestern Baptist Theological Seminary

Why do I give advice?

I still remember the day when I arrived at Chicago O’Hare airport on September 15, 1967. After checking into my room at International House, tears came down my eyes. My first time alone, so far away from home with no friends near by, I experienced a feeling of helplessness. I tried to seek advice and help from many people who had come to the US before me. Now almost thirty-five years later, with a wife of 33 years and two adult sons, a good statistical career, I feel totally at home in this adopted homeland.

This issue is the last one under the editorial leadership of Dr. Sue-Jan Wang. She has been a faithful supporter of the Washington DC seminar group that I started in 1990, and she took over the responsibility as the editor-in-chief of ICSA Bulletin under my presidency of ICSA in 1999. I was involved in the ICSA business as a board-director since 1991 for three 3-year terms and attended all the board meetings. During my term of presidency, ICSA started the first Student Awards and Travel Fellowship for the ICSA Applied Statistics Symposium, agreed to move the Symposium meeting site to other places away from the East Coast, and for the first time offered a reduced fee for statisticians residing in developing countries. I have enjoyed my service to the ICSA, including establishing a journal donation service for the libraries in China...

I organized several times mentoring sessions at the ICSA meetings. I also gave a mentoring talk during the ICSA Applied Statistics Symposium two years ago. When Dr. Sue-Jan Wang asked me to summarize my talk given there, I began to reflect on these 35 passing years again. What of my experience could be beneficial to the new generation of students from China? How could I help them to adjust to this new land?

How important are having good mentors?

I had good mentors during my first career in the past 35 years. Professor Stephen Fienberg, my dissertation advisor, was very helpful in guiding me to work on the problem about missing incomplete data in categorical data. Dr. Edmund Gehan, my mentor at M. D. Anderson Cancer Center for five years, helped me understand the issues in cancer research and statistics. Dr. Richard Simon, my boss at National Cancer Institute for nine years, worked together on methodology for cancer clinical trials, showed me the responsibility of a researcher at a governmental granting agency, and provided me a good example of success through hard work. I regard myself as extremely fortunate to have them as my mentors; from them and others I have learned a great deal.

Nonetheless, if I could do it all over again, I would try to learn more and get more help from my mentors. Having good mentors is one of the most important factors for a successful career. This fact is confirmed repeatedly in different studies of the sociology of science. To have a good mentor, one needs to have a learning attitude and an ability to work hard. Besides actual people as mentors, one can also learn a lot from books. Advice to a Young Scientist (Harper and Row, 1979), write-

What are the American values? When my sons were growing up, I tried to help them to develop their potentials fully. I encouraged them to study what they love, according to their interests. They were not brilliant, but they were diligent, with a sense of purpose and the power to concentrate. They enjoyed experiments either with hand or in mind. They cultivated a love for discovery and originality. They were reminded to persevere and not be cast down by adversity. They were born and grew up in America, so they appreciate American idea of freedom and believe in the inherent worth of every man and woman. We as parents acted as custodians and facilitators then, and now as friends and encouragers.

My wife and I grew up in Taiwan and came to the US for graduate study. We have lived more years here than in Taiwan or China. We come to realize that there are important characters and values, which shaped the American society. During the seventeenth century, immigrants from Europe settled in the New World for the opportunity of a better life and religious freedom. The US was and still is a country of immigrants. American people cherish optimistic and can-do spirit, individualism, entrepreneurship, and pragmatism. They appreciate self-help, self-improvement, and self-education, and the reward is usually appropriated by competence and merit. Since the freedom of speech is considered the fundamental liberty, the ability and boldness to communicate are highly valued. The backbone of all these manifestations is found in the religion of Judeo-Christian faith. Liberty, equality, and charity are considered as basic moral values derived from the religious faith. Therefore, people contribute their volunteering effort and form association to work for the common good.

How to be a good researcher? To enjoy our lives in the America, besides appreciating and adopting the American values, we have to do a good job in our profession as statisticians. Individually we need to manage our own time wisely. Everyone is given equally the same twenty-four hours per day; successful people don’t waste their time. We need to be diligent in our reading and learning, not only in statistics, but also in the general culture. We also need to project good appearance, maintain certain attentiveness, and seek visibility and influence. Collaboration and networking are essential, so it is important to be able to work with others in a congenial spirit. Contributing our time and effort to review and edit journals and to organize programs for the professional societies, such as ICSA and ASA are our responsibilities and privileges.

If one chooses an academic and research career, there are some useful guides for the whole scientific career. A Chicago Guide to Your Academic Career: A Port ’94 (2nd edition, 1994) by RRH Anholt, is a good book. Smart Speaking (Plume, 1992), by L. Schloff and M. Yudkin, is good for oral communication in general.

Related to the communication is the ability to teach. For those who elect the academic career, the following two books will be useful for improving teaching skills. Classroom Assessment Techniques: A Handbook for College Teachers (Jossey Bass, 2nd edition, 1994), by KP Cross and TA Angelo, is a good resource in the series for teachers. McKeeachie’s Teaching Tips: Strategies, Research, and Theory for College and University Teachers (DC Heath & Co, 11th edition, 2001), by WJ McKeeachie and G Gibbs, is a standard reference.


How to conclude a life? Above is a summary and a revision of the talk I gave at 2000 ICSA Applied Statistics Symposium. After working thirty years as a full-time statistician in academy, industry, and government, my experience could be useful to the new generation of Chinese students. I do not claim that I have learned all I could or I have practiced all I learned. In fact, just started my second career as a Christian theologian beginning with a graduate study toward a P.D. degree. I now have a second chance to practice what I said here.

We are reading more and more about elderly Americans going back to college to learn new things and enjoy their golden years. Many college special programs catered to the senior adults. Even many senior communities are sprung up near college campuses. Life long learning is definitely a possibility and becoming a reality. We could really have two productive careers. It all depends on whether we are willing to learn and try new things. If we do, we can enjoy our lives to the fullest as endowed by our Maker.
What do I know about the pharmaceutical industry?

Chiayu Lin, MPhil
Institute of Statistical Science, Academia Sinica
Taipei, Taiwan

Though the pharmaceutical industry has been in history for decades, and it is one of the top businesses in the U.S. recently, I got to know deeply about this industry as a freshman about 3 months ago. Here I'd like to share what I know and what I feel about the pharmaceutical industry from the standpoint of being a biostatistician.

The scientists spent plenty of time exploring a compound that may have potentially therapeutic effect to improve the quality of human lives by the means of shortening the duration of disease/disorder syndromes and of prolonging the human lifetimes.

The process that a compound has to go through in order to be accepted safe for human usage is multi-stage and multi-disciplinary, and that includes the manufacture and storage of the substances, pre-clinic tests of toxicity, animal studies of allowable safe doses, human clinical trials of efficacy and safety, and post-market test of drug comparisons and future safety concerns. To ensure the strength, purity, effectiveness, safety of the substance, several authorities set up the corresponding specifications and regularities at each stage. It is multidisciplinary because it takes scientists, medical doctors, and biostatisticians to tradeoff among many standards, which even involves in the ethics and finance.

Nothing is 100\% for sure to have no harm to the human bodies; yet the effort input to the pharmaceutical industry is a tradeoff between benefit and risks. Besides, there exist individual differences. However, from the viewpoint of being a biostatistician, it is a shame to say that we love to make conclusions for the majorities while only based on small sample evidences, which are generally of little confidence. However, it could be said that it would be improved if there were more studies conducted. Nevertheless, it is general infeasible due to a couple of reasons. Firstly, it is time-consuming. The average time period for a compound to be classified as a drug on the market is about 12-15 years, and the average life time of human beings is around 65-75 years. Additional, not all but small percentage of substances explored is eligible to be on the market. Secondly, it is a money-driven business. A single study run during the potential compound and/or the new drug investigation takes only a small percentage of the total cost. Besides, for the sake of economic balances and the timer of the disease, it is preferred to have drugs on market as soon as possible.

Therefore, one solution in this industry is to pick up the minimum benefit and the maximum cost/risk while conditioning on the achievement of baseline benefit. The maximum tolerable dose level is picked up for the sake of safety, and the minimum relieve of disease symptoms is depicted to evaluate the population efficacy of the drug. One concern of this viewpoint is that individuals make decisions of whether to take the drug based on individual benefit and risk. Even if for the viewpoint of social health welfare, it seems more likely that some patients would not be properly cared due to the high cost of treatment, while comparing the benefit-risk ratio among diseases.

While the economic issue belongs to pharmacoeconomists, what a biostatistician could do about it? One way is to improve the computation of the minimum sample size of a study in order to detect the clinical effectiveness with the maximum power, as well as the study designs. The other way is to improve the specification at each drug-development stage to ensure the effectiveness of the drug as it is claimed. It is no doubt that the design plays the most important role in a study. The selection of it depends on the hypothesis of interest, the sample size and the budget, as well as the efficiency and optimality of the test statistics.

At the end of a study, the statistical conclusion about a hypothesis testing is carried out, thereafter, of concern would be whether to schedule the following study or whether to market the drug. And the primary concern would fall in the category of being unable to reject the null hypothesis. While it happens it is not said that the null hypothesis is accepted, yet data does not provide enough evidence to reject it. If the data is representative, then the failure to reject the null hypothesis means that the probability of making the wrong conclusion that the drug is effective while the it is not is over 5\%, say, and the probability of making the wrong conclusion that the drug is not effective while it is less than 20\%, say. It sounds like that the potential drug has effectiveness with higher possibilities than it has no. At this moment, while the re-enrollment of patients in this study is not possible, how certain could it be to draw conclusions that the drug is ineffective and it should be abandoned. What value would p-value of an efficacy test be such that no further investigation would be necessary? It may be a good idea to suggest that when α=β. Then when does α=β?

Two examples are considered.

(1) Normal distributed data
Assume \( \mu_0 \) and \( \mu_1 \) are two independent sample means, and of interest is to test

\[ H_0: \mu_0 = \mu_1 \quad \text{vs.} \quad H_a: \mu_0 \neq \mu_1 \]

then the type I error

\[ \alpha = \Pr(T > c_0 | \mu_0 = \mu_1) = \Pr(T > c_0 | \mu_0 = \mu_1) \]

and

\[ \beta = \Pr(T < c_0 | \mu_0 = \mu_1) \]

thus, \( \beta \) can be solved from the table of t distribution.

(2) Binary data
Assume \( p_0 \) and \( p_1 \) are two independent sample proportions, and of interest is to test

\[ H_0: p_0 = p_1 \quad \text{vs.} \quad H_a: p_0 \neq p_1 \]

The test is to reject

\[ p_0 > p_1 > 0 \]

Z_{0.025} \sqrt{\frac{1}{n_0} + \frac{1}{n_1}} \]

then

\[ Z_{0.025} = \sqrt{\frac{1}{n_0} + \frac{1}{n_1}} \]

\[ \alpha \]

Thus, \( 0.025 \) can be located by standard normal Z distribution.

In both cases, it is claimed that no further investigation of the compound would be conducted if the p-value of the current trial is larger than the \( \alpha \) or \( \beta \) value computed.

Another solution is to wait for more the same studies being conducted and to com-
bine small studies to make the conclusion. And that raises the importance of meta-analysis.

While there exists only study population difference among phase I-IV clinical trials, whether it is a good idea to test the result of previous phase of clinical trials as prior information to test the efficacy of the current trial? This answer is positive and has been looked into by several articles. On the other hand, the bridging study claims to waive phase I and II studies while the new drug investigation is completed and passed at one country and is conducting at another one and several criteria have been met. The use of it is controversial, primarily due to the representa-
tiveness of the new population by the original population.

The lengthy scientific process for a compound to provide promising effectiveness could be shortened by the study of bioavailability, which compares the therapeutic equivalence by testing the rate or the extent to which the drug becomes available at the site of the body between/among different formulations of a drug. This equivalence test is different from the conventional equality test by a selection of a clinically meaningful difference, and the null hypothesis is rejected if the absolute value of the test statistics minus some meaning differ-
ence is small enough, i.e. of interest is to test

$$H_0: \mu_1 = \mu_2 \geq \delta$$ vs. $$H_1: \mu_1 = \mu_2 < \delta$$.

The pharmacokinetic model of the drug absorption, distribution, metabolism, and elimination is assumed. This is the main factor that causes individual difference in the response to drugs. A preferred design is to treat each individual as a block to receive all/partial formulations of interest, and to separate treatment periods by an enough long period of time to have previous drug effect washed out. This is the so-called crossover design. A 2-by-2 crossover design estimate the drug effect by taking the intra-subject effect while a higher order crossover design is useful to consider the inter-subject effect. Besides carryover effect, it is also of concern that whether the sample size of sequences is equal.

While the drug product is ready to be on the market, how long its potency could be of certain within 90%, say, of the label claimed. Stability study estimates the rate of degradation of the drug potency, say $$\beta_1$$, and picks up the time that is the intersection of the 95% lower bound of the degradation curve with the horizontal line of 90% label claimed to be the expiration date.

Mathematically, it is written as follows.

The working-Hotelling 100x(1-$$\alpha$$)% confidence lower bound for $$Y = \beta_0 + \beta_1 X$$ is a hyperbola

$$L = \beta_0 + \beta_1 X - \sqrt{\text{Var}(Y)} \sqrt{(1 - 2x^2)(2x^2 - 1)}$$

and \( \text{MSE} = \frac{2\text{SSE}}{(n-2)} \).

The expiration date is the solution of $$X$$ which satisfies the above equation while L is replaced by 90%. In other words, with mass production, if the drug product is stored properly, then the expiration date is the date on which we have 95% of confidence to conclude that the drug potency is 90% of the label claimed. This is critical, since relative humidity and weather temperature vary across regions and countries.

This article is one viewpoint of the author’s as a freshman in the pharmaceutical industry. Many important issues in the pharmaceutical industry may not have been viewed by the author yet while many issues pointed out in this article may have been looked into by many other articles. The author is thankful for Dr. Shin-Chung Chow for his consultation and recommendation of submitting to the ICSA bulletin.
From Meredith G. Warshaw

From the Warshaw's Field Guide to Atypical Statistics*

- Box plot: a cabal planning to hide surreptitiously all data contrary to the investigator’s hypotheses in a box for burial.

- Clinical trial: malpractice suit.

- Data cleaning: eliminating dirty data that will make scatter plots scatter and p-values nonsignificant.

- F-distribution—the proportion of students flunking Intro to Stats.

- Histograms: plots that cause sneezes and other allergic reactions in researchers.

- Logistical regression: a way of figuring out the logistics of getting your study accepted into JAMA.

- Nonlinear regression: what happens to the behavior of an investigator in the midst of preparing a grant submission.

- P-value: results of urinalysis.

- Survival analysis—strategizing how to get the most money from the funding agency so that your research center doesn’t fold.

- Z distribution—the proportion of students staying awake in Intro to Stats.

- Principal proponent’s analysis—figuring out what the principal investigator for the study wants to find. Alternatively, figuring out what the main supporter of the grant on the funding agency’s review committee wants to hear.

*Meredith G. Warshaw, Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), spent 10 years as a biostatistician doing psychiatry

Today’s Thought

A medium, so called because it is neither rare nor well done—Ernie Kovacs

A committee is a group that keeps minutes and loses hours—Milton Berle

Thin people are beautiful but fat people are adorable—Jackie Gleason

From the Desk of the Editorial Working Committee

REGIONAL ACTIVITY

Taiwan
By C. Andy Tsao

Reaching Out: Trends, Organizations and Information Sharing

As in other part of the globe, the profession of statistics in Taiwan is in the process of redefining itself in the past few years. Some application domains are emerging astonishingly, for example, bioinformatics, data mining and biopharmaceutical industries. Their fast development often presents challenges and opportunity for statisticians. New organizations are established to serve these demands.

Center of Drug Evaluation (CDE), Department of Health Established in 1998, CDE plays a pivotal role in upgrading the efficiency and quality of the drug evaluation process and providing proactive support for Biotechnology and Pharmaceutical Industries in Taiwan.

URL: http://www.cde.org.tw/english/english.htm

Protech Pharmacesvices Corporation Founded in 1997, PPC is now one of the most established integrated CRO companies in the Asia-Pacific area. URL: http://www.ppcrco.com/

Chunghua Data Mining Society (CDMS) URL: http://cdms.stat.fju.edu.tw/

Journal of Data Science (JDS)
Do you think that statistics might well be renamed as “data science” and good applications and good problems should be of focus rather than just “good math”? If you think so, you are not alone. Here is a new journal dedicated to data science. URL: http://mpd.pagras.net/~mtcha/JDataScience/JDS-0.html

Hong Kong
By Hailiang Yang

Here I report some of the activities of 2002 from the Hong Kong statistical community. I apologize for any missing information.

International Conference on Applied Statistics, Actuarial Science and Financial Mathematics: The University of Hong Kong and The Hong Kong Polytechnic University are jointly organizing an International Conference on Applied Statistics, Actuarial Science and Financial Mathematics. This conference is to be held at the University of Hong Kong (December 17, 2002) and the Hong Kong Polytechnic University (December 18-19, 2002).

The chairman of the organizing committee are Dr. K.W. Ng and Professor K.L. Teo and the chairmen of the scientific committee are Professors Elsas Shiu and Howell Tong. Many leading experts and distinguished speakers will give invited talks, among whom are Hans Gerber, Marc Goovaerts, Tze Leung Lai, and Harvey Panjer. http://web.hku.hk/~icads/

Workshop on Probability with Applications to Finance and Insurance: This workshop is to be held at the University of Hong Kong from July 15-17, 2002. The members of organizing committee are: Inchi Hu, Bing-Yi Jing, Tze Leung Lai, Qi-Man Shao, Hailiang Yang, and Siu Pang Yung. More than 30 experts in both theoretical and applied probability are invited to given a talk. The workshop is initiated by Professor Tze-Leung Lai. Prof. Lai will visit the University of Hong Kong as C.V. Starr Professor from June to July 2002. http://www.hku.hk/math/
WELCOME NEW MEMBERS

We would like to welcome new members who joined between January and June 2002.

Garish Aras  Chris Assaid  George Avrinpattu  Warren Bao
Aizong Cai  William Brady  Chen Chen  Jingru Chen
Aiil Cheng  Danny S. Chang  Dustin Christelle  Teng-Chiao Chu
Jin Ding  Andrea Dynder  Tara Erb  Vladislav Fishman
Tracy Gmoser  Shu-Pang Huang  Yangxin Huang  Mohammad Hoque
Manzoor Hussain  Xinwei Dmal Jia  John G. Jiang  Haim-Chang Jou
Young S. Paul Kim  James Lee  Dong Li  Haihong Li
Jennifer Li  Zhiyan Liang  Chengan Liu  Jason Liao
Yanjing Liao  Genzhou Lin  Xianquan Luian  Brett Masser
Ralph Paul  Barry Rosen  Jihe Qian  Amy Qin
Lei Shen  Fan Shi  Snya S. Su  Xiaowo Sun
Yuhan Soo  K. Linda Tang  Chi-Hse Teng  Lan-Feng Tsai
David A. Van Dyk  Joel Waksman  Hansheng Wang  Lia Wang
Wenjin Wang  Guodong Wu  Jianrong Wu  Zhili Xiang
Yang Xie  Jin Xu  Paul Zhang  Zuxuan Zhang
Lue Ping Zhao  Huaqing Zhao  Jun Zhao  Bei Zhou
Honglin Zhou  Wenjiong Zhou

MEMBERS' ACTIVITIES

News from ICSA Members

Dr. Robert T. O'Neill, Director of the Office of Biostatistics, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, is the recipient of the 2002 Marvin Zelen Leadership Award in Statistical Science. This annual award, supported by colleagues, friends and family, was established to honor Dr. Marvin Zelen's (The Department of Biostatistics at the Harvard School of Public Health) long and distinguished career as a statistician and his major role in shaping the field of biostatistics. The award recognizes an individual in government, industry, or academia, who by virtue of his/her outstanding leadership, has greatly impacted the theory and practice of statistical science.

Professor Kung-Yee Liang, Department of Biostatistics, Johns Hopkins University, was elected as an Academic Member for the Academia Sinica, Taiwan on July 4th, 2002. One of Dr. Liang's major research contributions to the statistical and biomedical community is his work, co-authored with Professor Zeger, on Generalized Estimation Equations (GEE), an innovative tool for analyzing longitudinal and other types of correlated data.

Professor Ruyu Tay, Graduate School of Business, University of Chicago, was elected to as an Academic Member for the Academia Sinica, Taiwan on July 04, 2002. Dr. Tay has made many important contributions in time series analysis, especially in the area of financial econometrics.
International Chinese Statistical Association
Balance Sheet
As of June 30, 2002

INTERNATIONAL CHINESE STATISTICAL ASSOCIATION
Membership Application / Renewal Form (2002)

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Please make checks payable to I.C.S.A.
Mail this form and a check to: ICSA c/o Yi Tsong, Ph.D.
13215 Lazy Glen Lane
Herndon, VA 22071
U.S.A.
tsong@ceder.fda.gov

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ASSETS
Current Assets
Checking/Savings
  checking  4,014.45
  Savings-CD  31,164.84
Savings-Money Market  35,653.42
Total Checking/Savings  70,832.71

Total Current Assets  70,832.71

TOTAL ASSETS  70,832.71

LIABILITIES & EQUITY
Equity
Opening Bal Equity  81,934.16
Retained Earnings  -8,179.45
Net Income  -2,922.00
Total Equity  70,832.71

TOTAL LIABILITIES & EQUITY  70,832.71
RECENT NEWS: (publications, research or teaching activities, job transfer, awards or honors received, etc.)

SUGGESTIONS: