FRONTIER SCIENCE FOUNDATION HELLAS

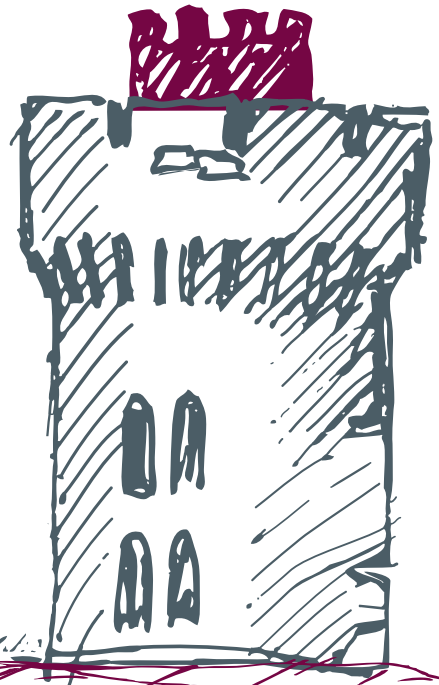
9th EMR-IBS and Italian Region Conference

Satellite Symposium
7-8 May 2017

SYMPOSIUM
honoring Professor
MARVIN ZELEN

Scientific Program

Book of Abstracts



The MET Hotel
Thessaloniki, Greece

Symposium Honoring
Professor Marvin Zelen

7-8 May 2017
The MET Hotel
Thessaloniki, Greece

Dear participants,

On behalf of the organizing committee, I would like to welcome you to the two-day Symposium ***in honor of Professor Marvin Zelen****.*

Marvin was a pioneer in the field of Biostatistics, Professor and exceptional member of the Harvard School of Public Health community, founder of FSTRF, but above all a mentor for scientists working in medical statistics and research.

His impact will be lasting not only through his seminal original scientific contributions but also through his mentoring of some of the most influential and original biostatisticians of today, who follow his example in producing work with great impact on society and public health.

All of us who had the privilege of knowing Marvin will always work to further his legacy.

This Symposium will celebrate his memory and unique contributions in science.

The current event is organized by Frontier Science Foundation-Hellas and co-sponsored by all Frontier offices. The Symposium is a satellite event of the 9th EMR-IBS and Italian Region Conference, which is also dedicated to Professor Zelen's legacy.

Thank you for joining us in honoring Marvin by celebrating Biostatistical Science.

Urania Dafni

Professor Marvin Zelen
1927-2014

Marvin Zelen was known as a giant in the field of biostatistics, as well as a man of vision, generosity, and warmth who served as a mentor to two generations of researchers.

Prof. Zelen was Lemuel Shattuck Research Professor of Statistical Science, at Harvard School of Public Health (HSPH), chair of HSPH's Department of Biostatistics from 1981-1990, and at Dana-Farber in the 1970s he helped create (and chaired through 1999) the Department of Biostatistics and Computational Biology. In all cases he led the growth of these programs to worldwide prominence and impact.

He had earlier formed the Statistical Laboratory at the University of Buffalo, which was dedicated to overseeing and improving the statistical aspects of large, complex drug trials. ECOG would go on to become one of the largest programs in the world for testing various cancer treatments. Another of Prof. Zelen's achievements was his establishment, in 1975, of the Frontier Science and Technology Research Foundation, a nonprofit devoted to advancing the use of statistical science and practice and data management techniques in science, health care, and education. Prof. Zelen served as president, and his wife Thelma was and remains chief administrative officer and board secretary. Prof. Richard Gelber said, "Their partnership is a role model of working together, and Thelma has been a major force in the formation and administrative leadership of Frontier Science as its chief operating officer for almost 40 years".

Prof. Zelen was known for developing the statistical methods and study designs that are used in clinical cancer trials, in which experimental drugs are tested for toxicity, effectiveness, and proper dosage. He introduced measures to ensure that data from the trials is as free as possible of errors and biases—measures that are now standard practice. Prof. Zelen helped transform clinical trial research into a well-managed and statistically sophisticated branch

of medical science, leading to significant medical advances such as improved treatments for several different forms of cancer. His research also focused on improved early detection of cancer; on modeling the progression of cancer and its response to treatment; and on using statistical models to help determine optimal screening strategies for various common cancers, especially breast cancer.

Throughout his long career, Prof. Zelen has been widely praised for his mentorship and generosity. His work has been recognized around the world through awards and other accolades. Noting just a few of them, in 1997, in honor of his 70th birthday, the School established the annual Marvin Zelen Leadership Award in Statistical Science, which has become one of the most prestigious honors in the field, meant to reflect Prof. Zelen's contributions to quantitative science and beyond. In 2009, Prof. Zelen was awarded the American Cancer Society's highest distinction—a Medal of Honor. A special issue of the journal *Lifetime Data Analysis* was dedicated to him in 2004. At least three symposia have been held around the world in his honor. He received an honorary doctoral degree from the University Victor Segalen in France, the Samuel S. Wilks Memorial Award—one of the most prestigious awards from the American Statistical Association—in 2006, and the Fisher Lecturer Award from the Committee of the Presidents of the Statistical Society (COPSS) in 2007 in recognition of his outstanding contributions to statistical science.

In short (quoting Prentice), Professor Marvin Zelen's work "did much to **define the biostatistical profession**".

Based on https://www.hsph.harvard.edu/news/features/in-memoriam-prof-marvin-zelen-a-tremendous-force-in-biostatistics/

Marvin and Thelma Zelen Assistant/Associate Professorship

The Marvin and Thelma Zelen Assistant/Associate Professorship was formally established to honor the enduring legacy of the Zelens and their countless contributions to the Department of Biostatistics, Harvard T.H. Chan School of Public Health.

Harvard requires we raise $3 million during the next 4 years to endow the Professorship; if we ultimately fall short, your gifts will be added to the Marvin Zelen Education and Statistical Leadership Award endowment, which funds the annual Zelen Leadership Award event and much-needed scholarships supporting the education of the next generation of biostatisticians.
We've received several large gifts to the professorship in the past year, but are still significantly short of our goal. We hope you will consider contributing to this fund.

www.hsph.harvard.edu/give

Be sure to specify the fund to which you are contributing either in the pull-down menu or the "Comments/Other Designation" field.

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Dimitris Karlis	*Athens University of Economics and Business, Greece*
KyungMann Kim	*University of Wisconsin-Madison, USA*
Victor Kipnis	*National Cancer Institute, USA*
Sharon-Lise Normand	*Harvard Medical School, Harvard T.H. Chan School of Public Health, USA*
Anastasios (Butch) Tsiatis	*North Carolina State University, USA*
L. J. Wei	*Harvard T.H. Chan School of Public Health, USA*

Invited Speakers

Su-Chun Cheng, *Department of Biostatistics, Harvard T.H. Chan School of Public Health, Dana-Farber Cancer Institute, USA*

Ori Davidov, *Department of Statistics, University of Haifa, Israel*

Laurence Freedman, *Gertner Institute for Epidemiology and Health Policy Research, Israel*

Constantine Gatsonis, *Department of Biostatistics and Center for Statistical Sciences, Brown University School of Public Health, USA*

Richard Gelber, *Harvard Medical School, Harvard T.H. Chan School of Public Health, Dana-Farber Cancer Institute, Frontier Science Foundation, USA*

Guadalupe Gómez, *Universitat Politècnica de Catalunya, Spain*

Ping Hu, *Biometry Research Group, National Cancer Institute, USA*

Mette Kalager, *Institute of Health and Society, University of Oslo, Norway*

Invited Speakers

KyungMann Kim, *Department of Biostatistics & Medical Informatics, University of Wisconsin-Madison, USA*

Victor Kipnis, *Biometry, National Cancer Institute, USA*

Nuala McGrath, *University of Southampton, UK*

Cyrus Mehta, *Cytel Inc, USA*

Sharon-Lise T. Normand, *Department of Health Care Policy, Harvard Medical School, Department of Biostatistics, Harvard T.H. Chan School of Public Health, USA*

Meredith Regan, *Dana-Farber Cancer Institute, Harvard Medical School, USA*

Louise Ryan, *School of Mathematical and Physical Sciences, University of Technology Sydney, Australia*

David Schoenfeld, *Department of Biostatistics, Harvard T.H. Chan School of Public Health, USA*

Scientific Program

First Day (Sunday 7 May)	
13:00 - 13:30	**Registration**
13:30 - 16:00	**First Session** **Chair: Dimitris Karlis**
13:30 - 14:00	**Marvin's Legacy**
14:00 - 14:40	**Richard Gelber** A STEPP Up for Subgroup Analysis
14:40- 15:20	**Louise Ryan** Statistical Strategies for Big Data
15:20- 16:00	**Laurence Freedman** Standardization of Mortality Rates for Hospital Performance
16:00 - 16:30	**Coffee Break**
16:30 - 18:30	**Second Session** **Chair: Mira Marcus-Kalish**
16:30 - 17:10	**KyungMann Kim** Randomized Consent Design and the Hawthorne Effect
17:10 - 17:50	**Victor Kipnis** New Insights into the Effect of Covariate Measurement Error in Mixed Models
17:50- 18:30	**Ori Davidov** Testing for Inequality Constraints in Singular Models by Trimming or Winsorizing the Variance Matrix
20:00	**Symposium Dinner**

Scientific Program

Second Day (Monday 8 May)	
09:00 - 11:30	**First Session** **Chair: Urania Dafni**
09:00 - 09:30	**Thelma Zelen & Zelen Family**
09:30 - 10:10	**Guadalupe Gómez** Sample Size Considerations for Composite Endpoints
10:10 - 10:50	**Sharon-Lise T. Normand** Statistical Approaches to Quantifying Quality and Disparities in Mental Health Care
10:50 - 11:30	**Meredith Regan** Estimating Benefit of Adjuvant Endocrine Therapy for Early Breast Cancer Patients
11:30 - 12:00	**Coffee Break**
12:00 - 14:00	**Second Session** **Chair: KyungMann Kim**
12:00 - 12:40	**Ping Hu & Su-Chun Cheng** Planning Clinical Trials to Evaluate Cancer Screening Programmes
12:40 - 13:20	**Mette Kalager** Mammography Screening in the Era of Modern Treatment
13:20 - 14:00	**Nuala McGrath** A Randomized Controlled Trial of the Uthando Lwethu ("Our love") Intervention to Increase Couples' HIV Testing in Rural South Africa
14:00 - 15:10	**Lunch Break**

Scientific Program

Second Day (Monday 8 May)	
15:10 - 17:30	**Third Session** **Chair: Richard Gelber**
15:10 - 15:50	**Cyrus Mehta** Adaptive Designs for Confirmatory Clinical Trials
15:50 - 16:30	**David Schoenfeld** The Infrequent Bayesian: Two Applications of Bayesian Statistics to Applied Problems
16:30 - 17:10	**Constantine Gatsonis** New Approaches for Studying the Elusive Link of Tests to Patient Outcomes
17:10 - 17:30	**Closing Statements**

Symposium Honoring Professor Marvin Zelen

Abstracts

A STEPP Up for Subgroup Analysis

Richard Gelber
Harvard Medical School, Harvard TH Chan School of Public Health, Dana-Farber Cancer Institute, Frontier Science Foundation, Boston, MA, USA

Subgroup analyses of randomized clinical trials are problematic due to multiple testing issues, lack of power within subgroups, and multiple cut-points to define subgroups when a covariate of interest is continuous. However, avoiding subgroup analyses is a 'steep price to pay' because physician assessment of the magnitude of the treatment effect for an individual patient is critical to balance the benefits and burdens of therapy to personalize patient care. The Subpopulation Treatment Effect Pattern Plot (STEPP) method is a visual, non-parametric, exploratory approach to investigate treatment effect heterogeneity in clinical trials. STEPP will be described and applied to clinical trials where survival is the primary endpoint. Recent extensions of STEPP to analyze binomial, count, and continuous endpoints, as well as an application for meta-analysis (Meta-STEPP) will be presented. The International Breast Cancer Study Group (IBCSG), the Breast International Group (BIG), and the Aspirin/Folate Polyp Prevention Study Group provided clinical trial data for examples.

Statistical Strategies for Big Data

Louise Ryan
School of Mathematical and Physical Sciences,
University of Technology Sydney, Australia

The statistics profession is in a period of disruptive change, heralded by explosive growth in information technology and the "big data" revolution. New specialties such as machine learning, data science and analytics seem to go from strength to strength and sometimes it seems like statistics is being discarded like one of last decade's fashion embarrassments. Visionaries like Professor Zelen of course anticipated all this years ago, but I unfortunately the profession as a whole didn't listen. In this presentation, I will offer some perspectives on the changing landscape for statistical science. I'll draw on some of my own recent projects where "statistics as usual" falls short and outline some of the areas where I think there are great opportunities for our profession to strengthen our role in the data science arena. I'll finish up with some thoughts about implications for training the next generation as well as up-skilling the current generation of statisticians. My presentation will be similar to the one I presented a few weeks ago for the Presidential Invited Address at ENAR.

Standardization of Mortality Rates for Hospital Performance

Laurence Freedman[1], Ronen Fluss[1], Nethanel Goldschmidt[2] and Micha Mandel[3]

[1] Gertner Institute for Epidemiology and Health Policy Research, Tel Hashomer, Israel

[2] Ministry of Health, Jerusalem, Israel

[3] Hebrew University, Jerusalem, Israel

When monitoring hospitals with regard to performance measures, it is now commonly accepted that some type of standardization be used to adjust for the distribution of profiles of patients treated at the hospital. In the epidemiologic literature two main types of standardization are described – direct and indirect. While direct standardized rates of different hospitals may be compared, the prevailing wisdom is that indirect rates are not strictly comparable. On the other hand, standard implementation of the direct method to the data of small hospitals is problematic, leading to large variances in the standardized rates. Perhaps because of this, in monitoring hospital performance indirect standardization is the more commonly used method. In this talk, we explore different methods of standardization and their advantages and disadvantages, illustrated by data on 30-day mortality after acute myocardial infarction in Israeli hospitals. The work is being carried out as part of the preparation for a new initiative of the Organisation for Economic Co-operation and Development (*OECD*) to monitor hospital performance in OECD countries.

Randomized Consent Design and the Hawthorne Effect

KyungMann Kim
Department of Biostatistics & Medical Informatics,
University of Wisconsin-Madison, USA

Randomized consent design was first proposed by Zelen in 1979 as an alternative to randomized clinical trials in some settings. Proponents of this design often argue that the randomized consent design is justified because it eliminates the so-called Hawthorn effect and resentful demoralization in the control arm. Although the aim of this design was to increase recruitment by avoiding some of the problems associated with obtaining informed consent, this method is ethically controversial because consent for randomization is not sought. Besides the ethical issues of not informing patients, there are other potentially serious issues regarding the confounding and resultant bias in treatment comparison. This is particularly so in behavioral intervention trials, where investigators are often tempted to use such designs to save recruitment cost for concurrent trials that enroll the same patients. There is not only the issue of the placebo effect in such designs, but also the Hawthorn effect could muddy the comparisons. Therefore, based on a randomized consent design with control and intervention which results in three distinct groups, we show using very simple statistical contrasts why unbiased comparison is impossible due to confounding and self-selection.

New Insights into the Effect of Covariate Measurement Error in Mixed Models

Victor Kipnis
Biometry, National Cancer Institute, USA

Mixed effects models have become one of the major approaches to the analysis of longitudinal studies. Random effects in those models play a twofold role. First, they reflect heterogeneity among individual temporal (fixed) effects, and, second, they induce a correlational structure among temporal observations of the same subject. If both the exposure and outcome vary with time, it is natural to specify mixed effects model for both. If heterogeneity in temporal effects for exposure and outcome are influenced by related factors, the corresponding random effects will be correlated, inducing correlation between random effects in the outcome mixed model and the exposure. In this case, there are three different effects of the exposure on outcome, the within-subject or individual level effect, the between-subject effect, and the marginal or the population-average effect. If ignored, the estimated exposure effect will be biased for either effect. If exposure is measured with error, the naive model that is specified by using the measured exposure in place of the true one, will always have a nonzero correlation between random effects in the outcome model and measured exposure, even if this correlation was zero in the model with true exposure.
It is therefore critical to allow for the correlation between random effects and the exposure. We suggest doing so by specifying simultaneous mixed effects models for outcome and exposure with correlated random effects. The adjustment for measurement error in such simultaneous models would provide consistent estimates for all three possible exposure effects under the condition that given true within - and between - subject exposure, the corresponding decomposition of error-prone exposure is not related to the outcome. The theory is exemplified using data on physical activity as measured by accelerometer on sleep efficiency in a longitudinal study together with the results of some simulations.

Testing for Inequality Constraints in Singular Models by Trimming or Winsorizing the Variance Matrix

Ori Davidov
Department of Statistics, University of Haifa, Haifa, Israel

There are many applications in which a statistic follows, at least asymptotically, a normal distribution with a singular or nearly singular variance matrix. A classic example occurs in linear regression models under multicollinearity but there are many more such examples. There is well-developed theory for testing linear equality constraints when the alternative is two-sided and the variance matrix is either singular or non-singular. In recent years there is considerable, and growing, interest in developing methods for situations in which the estimated variance matrix is nearly singular. However, there is no corresponding methodology for addressing one-sided, i.e., constrained or ordered alternatives. We develop a unified framework for analyzing such problems. Our approach may be viewed as the trimming or winsorizing of the eigenvalues of the corresponding variance matrix. The proposed methodology is applicable to a wide range of scientific problems and to a variety of statistical models in which inequality constraints arise. We illustrate the methodology using data from a gene expression microarray experiment obtained from the NIEHS' Fibroid Growth Study.

Sample Size Considerations for Composite Endpoints

Guadalupe Gómez
Universitat Politècnica de Catalunya, Spain

Randomized clinical trials (RCT) provide compelling evidence that a study treatment causes an effect on human health. A primary endpoint (PE) ought to be chosen to confirm the effectiveness of the treatment and it is the basis for computing the number of subjects needed in the RCT. Often a Composite Endpoint (CE), E*, based on a combination of individual endpoints, E1, E2, is chosen as a PE. As a tool for a more informed decision between using the CE as PE or one of the components or the CE, Gómez and Lagakos (Statistics in Medicine, 2013) proposed the ARE method for time-to-event endpoints and Bofill and Gómez (submitted) extended the method to binary endpoints. The ARE method uses the asymptotic relative efficiency (ARE) between two possible tests to compare the effect of a treatment: one test based on a single endpoint and the other based on the CE. At the design stage of a RCT and in a setup where two candidate endpoints E1 and E2 or their composition E* are potential PE, the computation of the sample size for each endpoint is needed. Computation of the sample size for individual outcomes has been widely studied and different versions are routinely used. Computation of the sample size for composite endpoints taking into account the joint behavior between E1 and E2 are rarely provided. We will present formulations for the required sample size to detect a given treatment effect in the primary endpoint when is defined as the composite endpoint E*, for a given significance level and power, in a variety of scenarios and for both binary and time-to-event endpoints. In both cases marginal prevalences and marginal treatment effects are assumed, the latter given either by constant hazard ratios for times to E1 and E2 or by odds ratio for the occurrence of E1 and E2. Difficulties due to the non constant hazard ratio or to the complex expression of the odds ratio of the composite endpoint will be discussed.

Statistical Approaches to Quantifying Quality and Disparities in Mental Health Care

Sharon-Lise T. Normand
Department of Health Care Policy, Harvard Medical School
Department of Biostatistics, Harvard T.H. Chan School of Public Health, USA

The last two decades have been characterized by an increasing focus on healthcare provider performance measures, most often utilizing multiple binary response outcomes. In this problem, data arise from multiple clusters where (a) outcomes within clusters are more similar than outcomes between clusters; (b) within-cluster covariates vary across clusters; (c) clusters are observed repeatedly over time; and (d) multiple binary measures are observed for each unit within the cluster. In this talk, we describe methods to determine whether quality of care in schizophrenia care varies by race/ethnicity and over time; and (b) whether these patterns differ across counties within states using Medicaid claims data from California, Florida, New York, and North Carolina during 2002–2008. Random effects approaches for handling within-county correlation and item response theory models for handling multiple binary outcomes per beneficiary are used to determine if where you live matters.

Thanks: Marcela Horvitz-Lennon (Rand Corporation), Rita Volya (Harvard Medical School), Rachel Garfield (Kaiser Family Foundation), Julie Donohue and Judith Lave (University of Pittsburgh Graduate School of Public Health).

This research was supported by R01MH087488 from the National Institute of Mental Health.

Estimating Benefit of Adjuvant Endocrine Therapy for Early Breast Cancer Patients

Meredith Regan
Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

Adjuvant endocrine therapy is a mainstay of treatment for patients with endocrine-responsive early breast cancer. Questions remain concerning which patients should receive what type of endocrine therapy and for how long. Several factors have been considered as potential indicators to predict benefit of endocrine therapy, including patient factors, clinico-pathological factors and multigene assays. To date, the risk of recurrence is the primary consideration for breast cancer adjuvant therapy recommendations. Three International Breast Cancer Study Group (IBCSG)-led phase III trials of adjuvant endocrine therapies – BIG 1-98 for postmenopausal women, and SOFT and TEXT for premenopausal women – provide the opportunity to estimate outcomes according to risk of recurrence and shed light on who should receive which type of adjuvant endocrine therapy and for how long.

Planning Clinical Trials to Evaluate Cancer Screening Programmes:
Dedication to the memory of Professor Marvin Zelen

Ping Hu
Biometry Research Group, National Cancer Institute, USA

This presentation provides a brief overview of the concepts and statistical models for planning clinical trials to evaluate cancer screening programmes. The aims of this presentation are: i) to propose a new method to estimate the forward recurrent time in planning clinical trials, and ii) to show how the estimated parameters can be applied to plan future screening trials. Prof. Marvin Zelen was one of the first who developed statistical theories to serve as a basis for the design of clinical screening trials. Zelen's 1993 Biometrika paper and his two subsequent articles co-authored with his students are discussed. Prevalence, incidence, mean sojourn time, and mean forwarded recurrence time are estimated by the proposed methods. Applications are made to recent screening trials for the early detection of lung cancer. The US National Lung Screening Trial (NLST) data set is used for illustration.

A Randomized Controlled Trial of the Uthando Lwethu ("Our love") Intervention to Increase Couples' HIV Testing in Rural South Africa

Nuala McGrath
University of Southampton, UK

Background: Couples-based HIV testing and counseling (CHTC) is an effective strategy for reducing sexual transmission between partners. However, uptake of the service has been low. We tested the efficacy of a couples-based intervention to increase participation in CHTC in a high HIV-prevalence setting. Methods: We randomized 332 couples (664 individuals) from a rural community in KwaZulu-Natal South Africa for a randomized controlled trial of a couples-based behavioral intervention comprising either six sessions (two group sessions/four couple counseling sessions) (n=168 couples) vs one group session (n=164 couples). The intervention explored barriers to HIV testing and promoted improved communication skills and relationship dynamics. The primary outcomes were participation in CHTC and number of reported unprotected sex acts in the last 90 days with primary partner. Couples were ineligible if they had mutually disclosed their HIV status or previously participated in CHTC. Results: 22 couples (6%) were lost-to-follow-up before 9 months, with no difference by group, p=0.36. Using intent-to-treat analysis, at 9-month follow-up, a higher proportion of intervention couples had participated in CHTC than control couples (42% and 12% respectively; p<0.001), with a shorter time to CHTC than control group couples who participated in CHTC (Logrank p<0.0001). For sexual behavior, a negative binomial regression model accounting for couple clustering found no significant group-by-time interaction in the proportion of unprotected sex acts (p=0.08). Conclusion: This is the first intervention that targeted increasing participation in CHTC. Results suggest that addressing relationship factors among African heterosexual couples can improve uptake of CHTC. Our intervention reached a high number of couples that were unaware of their joint HIV status at baseline. Further, results show that it is possible to promote engagement in CHTC-- which is an effective strategy that accomplishes HIV testing, mutual disclosure and can facilitate entrée into treatment for HIV-positive individuals in high prevalence settings.

Adaptive Designs for Confirmatory Clinical Trials

Cyrus Mehta
Cytel Inc, USA

Adaptive designs have been proposed as a means to increase the efficiency of randomized clinical trials, potentially benefiting trial participants and future patients while reducing costs and enhancing the likelihood of finding a true benefit, if one exists of the therapy being studied. These designs can modify the future course of an on-going trial, by applying prospectively specified decision rules to the unblinded interim data, without undermining the validity of the final analysis. Typical design changes implemented in a confirmatory setting are sample size re-assessment, dropping of non-performing treatment arms in a multi-arm study, and changes in the inclusion/exclusion criteria with special reference to biomarker based population enrichment. An example of each such design type will be presented, drawn from our consulting experience at Cytel. Type-1 error control, operational and regulatory considerations will be discussed.

The Infrequent Bayesian: Two Applications of Bayesian Statistics to Applied Problems

David Schoenfeld
Department of Biostatistics,
Harvard T.H. Chan School of Public Health, USA

Frequentist statistical inference is the stock in trade of a practicing biostatistician but sometimes Bayesian reasoning allow us to understand a problem more deeply. I will focus on two specific applications of Bayesian reasoning which can give insight in the design and analysis of clinical trials. The first is that it provides a way of quantifying the uncertainty of our knowledge due to the limitations in the amount of data we have analyzed. The second is that it provides a way of incorporating our prior beliefs in our understanding of the data we are analyzing. An example of the first type of reasoning is in study design in ALS. ALS investigators would like to conduct single arm phase II trials on new drugs and compare them to the placebo arms of previous clinical trials. Using a database with data from placebo groups for many trials one can calculate the predictive distribution of the results of a new placebo group and use it to calculate the criteria for what would be a significant effect, as well as the sample size to detect this effect. Surprisingly, unless the hypothesized treatment difference was very large, a historically controlled trial will require more patients than a randomized trial! Thus, historically controlled trials should be reserved for situations where the treatment effect was large enough to be easily appreciated. An example of the second type of reasoning concerns whether a cancer therapy that improves tumor free survival also improves overall survival. Many cancer trials don't have enough data on overall survival because of the decision to stop the trial when it is positive in terms of time to tumor progression. Cancer trialists do this when they believe that the treatment will not have a large effect on time from progression to death. Our approach is to develop a joint model of time to tumor progression and time from tumor progression to death. Then Bayesian estimates of the effect of treatment on overall survival can be calculated as a function how strongly the trialist believes that the treatment effect on the time from progression to death is small. These examples show some of the potentials of Bayesian reasoning in biostatistics and suggest that biostatisticians should teach Bayesian statistics to other health care professionals whenever we have the opportunity.

New Approaches for Studying the Elusive Link of Tests to Patient Outcomes

Constantine Gatsonis
Department of Biostatistics and Center for Statistical Sciences, Brown University School of Public Health, USA

The question of evaluating the effect of a medical test on subsequent patient outcomes has proved to be particularly challenging. Insofar as a test provides information, which is subsequently incorporated into further diagnostic and therapeutic decision making, its impact is strongly affected by the intervening decisions about medical care. In this presentation, we will focus on recent approaches to the study of the impact of tests, which include the analysis of data from large secondary databases and registries and data from randomized studies with adjustments for confounding.

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