TEL AVIV UNIVERSITY אוניברסיטת תל-אביב

The Department of Statistics and Operations Research,
The School of Public Health,
The Mortimer and Raymond Sackler Institute of Advanced Studies,
In cooperation with the Israel Statistical Association

Are pleased to invite you to a special meeting on

Clinical Trials and Clinical Research

Hosting our honorary guest,
Tel Aviv University Sackler Lecturer, 2011-2012

Prof. Marvin Zelen
Harvard University

The meeting will take place on **15 December 2011**, from 14:00 to 18:00

at the **Diaspora Museum (Bet Ha-Tfutsoth), Zeevi Auditorium**.

Program:

13:30 Light refreshments

14:00 Welcoming remarks, Prof. David Steinberg, Chair, School of Mathematical Sciences, Tel Aviv University

14:10 Prof. Marvin Zelen, Harvard University
Are Multi-Center Randomized Clinical Trials Being Analyzed Incorrectly?

14:40 Dr. Anat Sakov, Teva Pharmaceutical
Statistical Challenges in the Development of BioSimilar Drugs

15:10 Dr. Ruth Heller, Tel Aviv University
False Discovery Rate Controlling Procedures for Discrete Tests

15:40 – 16:10 Coffee Break

16:10 Prof. Laurence Freedman, Gertner Institute for Epidemiology and Health Policy Research
Concepts and Challenges in Combining Dietary Biomarkers with Self-report in Nutritional Epidemiology

16:40 – 18:00 Panel Discussion:
Future Challenges for Clinical Trials, in view of Personalized Medicine and Converging Technologies
Organizer and Chair: Dr. Mira Marcus-Kalish, Tel Aviv University
Panelists: Prof. Marvin Zelen, Department of Biostatistics, Harvard University
Dr. Ron Neuman, Corporate Medical Director, Teva Pharmaceutical Industries Ltd.
Dr. Raanan Berger, Director, Division of Medical Oncology, Sheba Medical Center
Prof. Yoav Benjamini, Dept. of Statistics and OR, Tel Aviv University

Abstracts

Are Multi-Center Randomized Clinical Trials Being Analyzed Incorrectly?

Marvin Zelen
Department of Biostatistics and
School of Public Health
Harvard University

Scientific evidence of the benefits (or harms) of therapies are widely accepted if the conclusions are based on randomized clinical trials. A prevailing philosophy is that all analyses should be guided by the design of the trial. Nevertheless, in practice, this philosophy is very much ignored. Three issues, basic to analyses, will be discussed. (1) Nearly all of the statistical methods require a random sample of patients from a well-defined population. However this is rarely the case. Consequently an inference dawn from a multi-center trial may not apply to a "population "with disease but only to the patients who entered the trial. (2) Rarely is center variability accounted for in an analysis. This is especially true when there are large numbers of centers which enter a very small number of patients in a trial. (3) Many trials are planned using permuted blocks, but this feature is ignored in the analysis. In this lecture, I will discuss some of these issues and describe how they can be dealt with.

Statistical Challenges in the Development of BioSimilar Drugs

Anat Sakov
Head of Biostatistics
Innovative R&D and BioSimilar
Teva Pharmaceutical

Generic drugs are a copy of a branded chemical drug, and their development is relatively short and cheap and typically includes only a small Phase 1 study. As a result, the approved generic drug is a low-cost product. The situation for biological drugs (e.g. proteins) is different. Because of their complexity, it is impossible to create an identical copy of the branded biologic drug, and they are expected to be only "similar". Hence, the clinical development of a BioSimilar drug is more similar to the development of a branded drug.

BioSimilar received a lot of attention lately in the US in order to reduce health care costs. Nowadays, there is a legal pathway to approve BioSimilar drug. However, there is still a vivid discussion on the scientific, including statistics, requirements which still need to be sorted and clarified.

In this talk, I will address some of the open statistically-related issues and challenges including the selection of endpoints, setting of margins, meta-analysis and more.

False Discovery Rate Controlling Procedures for Discrete Tests

Ruth Heller
Department of Statistics and Operations Research
Tel Aviv University

Benjamini and Hochberg (1995) proposed the false discovery rate (FDR) as an alternative to the FWER in multiple testing problems. Since then, researchers have been increasingly interested in developing methodologies for controlling the FDR under different model assumptions. For discrete data these procedures may be highly conservative. Incorporating the discreteness of the tests into the multiplicity adjustments may increase the power dramatically while maintaining the nominal FDR level. In this paper, we develop new discrete analogues to two multiple testing procedures that control the FDR: the Benjamini-Hochberg (BH) and the Benjamini-Liu (BL) procedures. We demonstrate large power gains of the discrete versions over the original versions. In addition, we examine procedures that modify the BH and BL procedures by exploiting the discreteness using the following two adjustments: application of Tarone's method that first removes null hypotheses with test statistics that are unable to reach a certain level of significance, and the use of midP-values. The suggested procedures have a realized FDR level closer to the nominal FDR level in comparison to the realized FDR level of the original procedures. Moreover, the discrete analogue to the Benjamini-Liu procedure is proved to control the FDR for independent test statistics for finite samples. We consider an application to pharmacovigilence spontaneous reporting systems, that serve for early detection of adverse reactions of marketed drugs.

Concepts and Challenges in Combining Dietary Biomarkers with Self-reports in Nutritional Epidemiology

Laurence Freedman
Gertner Institute for Epidemiology and Health Policy Research

Dietary measurement error causes serious challenges to detecting associations between diet and disease in epidemiological studies. Estimated relative risks are attenuated, and statistical power is reduced. Moreover, increasing the sample size provides only a partial remedy, since the attenuated estimates of relative risk are often as low as 1.10-1.25, and even when statistically significant, may be indistinguishable from the effects of unknown confounders. Methods to reduce error in dietary measurements are, therefore, of primary importance. We describe two statistical methods of combining self-reports and biomarkers that address this question. The first method, using principal components or Howe's non-parametric method has the advantage of simplicity but does not provide de-attenuated estimates of risk, not does it guarantee improvements in statistical power with adequate control for confounding. The second method, based on regression calibration, provides nearly-unbiased estimates of dietary-disease associations and a valid test of the null hypothesis of no association. In the case where the dietary-disease association is mediated by the biomarker, the association needs to be estimated as the total dietary effect in a mediation model. However, the hypothesis of no association is best tested through a marginal model that includes as exposure the regression calibration-estimated intake but not the biomarker. We illustrate the method with data from the Carotenoids and Eye Disease Study (CAREDS) and show that inclusion of the biomarker in the regression calibration-estimated intake increases the statistical power. Our development throws light on previous analyses of dietary-disease associations reported in the literature.

Panel Discussion
Future Challenges for Clinical Trials in view of Personalized Medicine and converging technologies

Advanced technology in medicine and clinical research has led to massive data capture, from multiple sources and various levels throughout the human body, high throughput analysis and thus creates major new challenges in designing and analyzing clinical trials.

This panel discussion will focus on these challenges, considering methodological, practical and economical issues for the short and long terms and debating the tradeoffs of harm versus benefits to individual health.

The "converging technologies" initiative (NSF 2003) relates to "the human being functioning in its surrounding as 1 operating system." That includes environmental, cultural and community effects combined with physiology, including brain research and behavioral functioning. The NSF initiative encouraged and provided the platform for multidisciplinary R&D involving almost all areas of science, providing new medical insights, understandings, tools and products, as well as massive amounts of information and data. Lately this initiative received some further tailwind from Alan I. Leshner, chief executive of AAAS and executive publisher of *Science*, and from an MIT white paper initiative presented by Nobel laureate Phillip Sharp, who claimed it is the "third revolution" in biomedical research (Jan. 2011).

The European Common Strategic Framework (vision 2020) recognized the need for clinical trial design to be a common effort of academia, industries and clinical partnership "to ensure safe and effective personalized medicine" The suggested focus was on Bio-banking of tissues and coordinated clinical electronic patient records and "omics" systems for biomarker discovery and rapid implementation into clinical practice. Furthermore along with the MRC and NIH the European Union has established ECRIN (European Clinical Research Infrastructure Network) involving 14 countries (with 9 additional countries about to join), an infrastructure designed to support multinational clinical research making Europe a single area of clinical trials. How will this framework affect existing discussions regarding clinical barriers to extrapolating from "on trial" patients to "real life"?

In parallel, we see more and more targeted research and discussions in the Predictive, Preventive and Personalized Medicine (PPPM) area, new professional associations, such as EPMA (European Personalized Medicine Association), the launch of journals and publications and the first world EPMA congress (Bonn Sep11). What new approaches and tools are needed to successfully support the PPPM research?

The promise, as expressed by Prof. Sharp and many others, is that this merging of distinct technologies, including life sciences, physical sciences and engineering, and the consequent support for PPPM, will eventually increase drug efficacy and thus will influence the economics of health care up to the vision of reducing world disparities, immigration, etc. Is it practically viable? Time will tell – and the panelists will have an opportunity to present their vision.

Our task is not to foresee the future, but to enable it." (Antoine de Saint-Exupéry, 1900–1944)