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STRATOS initiative – Guidance for designing and analyzing observational studies

STRATOS INITIATIVE

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Statistical methodology has seen substantial development in recent times. For example, techniques have been developed to handle problems caused by missing data and to counterbalance biases caused by measurement error, two issues occurring in many observational studies. In the context of survival data, analysis methods have been developed to investigate the effect of recurrent events or to conduct joint modeling of time-to-event and longitudinal changes to assess markers of disease progression. Unfortunately, many of these developments are often ignored in practice. Even worse, 'standard' analyses reported in the medical literature are often based on unrealistic assumptions or use unsuitable methods, casting doubt on their results and conclusions. To help bridge the gap between methodological innovation and applications, the STRengthening Analytical Thinking for Observational Studies (STRATOS) initiative was launched in 2013. It aims to provide statistical guidance for key topics in the design and analysis of observational studies. In practice, many analyses are conducted by researchers with limited statistical background. Consequently, STRATOS plans to develop guidance for researchers with different levels of statistical knowledge to help improve the statistical quality when analyzing data from observational studies (Sauerbrei et al 2014, www.http://stratos-initiative.org/).

Appropriate statistical methods are key to translating raw empirical data into new insights and deeper understanding of complex processes affecting human health, the economy, environment, etc. Yet, the complexities of such processes, and of the observable data they generate, create numerous analytic challenges. In the 21st century, progress in the theory of mathematical statistics and expansion of computational resources and technology led to rapid developments in statistical methodology, resulting in a large number of increasingly complex and more flexible statistical techniques and models. For example, the prediction of survival probabilities for patients with cancer or other diseases. In such applications, researchers are confronted with at least three interrelated 'main' statistical challenges (a) which variables are 'stronger' predictors of the outcome (more than 20 variable selection techniques have been proposed), (b) what functional form should be used to model continuous predictors (e.g., a linear relationship; categorization is popular, but the definition of the categories need to be determined; fractional polynomials have gained some popularity and many spline based approaches have been proposed) and (c) is the commonly used Cox proportional hazards (PH) model suitable (alternatives have been proposed including flexible parametric models) and is the PH assumption consistent with the data (extensions to models allowing time-varying effects exist). Methods to handle these interrelated challenges are available, but often these important developments are ignored in every-day practice of data analysis. Consequently, the design and analysis of observational studies, which can be complex and costly, may have serious weaknesses, resulting in misleading inferences and incorrect conclusions. For examples, see section 3.1 in Sauerbrei et al (2014).

During the last two decades several initiatives were started with the aim of improving the research process in the health sciences. Substantial progress was made concerning transparent and complete reporting in order for readers to be able to judge the usefulness of data, the suitability of the analysis and to interpret study results in the appropriate context. Several groups have developed reporting guidelines for different types of studies, with the EQUATOR network (www.equator-network.org) providing a repository for these guidelines (Simera et al 2010).

However, what is lacking is guidance for the design and analysis of observational studies where the improvement of research depends on better practical implementation of appropriate statistical methods. The STRATOS initiative has started to work on developing guidance which will cover issues such as improving the awareness of potential pitfalls due to inappropriate use of conventional methods, the choice of appropriate validated methods of analysis able to overcome specific challenges in the data and the identification of statistical software that can be used to implement these more advanced methods. It is one of the fundamental objectives of STRATOS to develop guidance for researchers with different levels of statistical

training, skills and experience. We will start with guidance which points to methodology that is useful for most experienced statistical researchers. Such guidance will then be adapted to educate applied researchers with less statistical knowledge, which may include clinicians and medical students. Finally, experts in specific areas will work to identify current gaps in knowledge and improve, validate and compare existing methods, which will then be incorporated into guidance for the other lower two levels.

To develop such guidance requires a well-structured, highly interactive collaboration between a large, international group of experts in statistical issues and methodology in clinical epidemiology, whose research combines development of new methodology with collaborative research on real-life applications and whose joint, complementary expertise covers different areas of statistical research. At present, particular challenges are being addressed by leading authorities in different areas of statistical research, but little effort is invested in making the results of these separate developments accessible and ensuring their application in practice. In addition, many researchers concentrate on developing new and more complicated methods, but knowledge about their properties and relative strengths and weaknesses is often inadequate, since meaningful comparisons of the available approaches are insufficient, and therefore evidence based guidance for users is lacking. As an example, triggered by the intention to derive suitable 'omics' predictors (often called gene signature) in high-dimensional data, various variable selection techniques were proposed during the last two decades, adding to the long list of more traditional approaches already available during the second half of the last century. Researchers need to choose one (or more) of these strategies to conduct an analysis. Meaningful studies, including simulations, are needed to compare these procedures, provide evidence on their advantages and disadvantages and develop recommendations to guide practicing researchers in selecting a suitable approach. This environment provided the motivation for, and driving vision behind, the STRATOS initiative.

STRATOS currently has nine topic groups (TGs) (Table 1), all of which include between 8 – 12 members. Further details are available in Sauerbrei et al 2014 and on the STRATOS website. Ten cross-cutting panels have been created to coordinate the activities of different TGs, share best research practices and disseminate research tools and results across TGs (Table 2). These panels address common issues such as creating a glossary of statistical terms, giving advice on how to conduct literature reviews and simulation studies and setting publication policies for the initiative. The recommendations of the cross-cutting panels are intended to support, integrate and harmonize work within and across the TGs and to increase transparency in producing guidance.

Summary and Outlook

STRATOS is an initiative that aims to provide statistical guidance for key topics in the design and analysis of observational studies. Statistical research, including simulation studies, is needed to assess competing statistical approaches which can then be used to develop such guidance. Ongoing research, discussions and activities within STRATOS are conducted in the nine topic groups and ten panels. The structure of STRATOS is designed to make the resulting guidance broadly useful through collaboration with clinicians, applied researchers, scientific societies and related projects and initiatives. STRATOS is focused on health sciences but is relevant for all areas of empirical science, e.g. econometrics, life and physical sciences, social sciences, engineering..

The emergence of "Big Data" is an additional issue relevant for STRATOS. However, big data poses particular challenges and opportunities and encompasses diverse areas and data sources. Therefore, STRATOS has decided that big data will not be a topic group by itself but will be considered and related to by all TGs.

To improve statistical methodology and its transparency, statistical researchers must put more emphasis on comparing competing strategies and must generate evidence to support state-of-the-art methodologies. They must also provide guidance that is appropriate for the large community of data analysts with wide range of statistical knowledge and experience.

In the next issues we will publish a series of short articles regarding each of the nine TGs. In each article we will give a general description of the TG, the aims of the group and a few examples that illustrate good statistical practice on the topic of interest.

References

Sauerbrei W, Abrahamowicz M, Altman DG, le Cessie S and Carpenter J on behalf of the STRATOS initiative. (2014) STRengthening Analytical Thinking for Observational Studies: the STRATOS initiative. Statistics in Medicine, 33: 5413-5432.

Simera I, Moher D, Hirst A, Hoey J, Schulz KF, Altman DG. Transparent and accurate reporting increases reliability, utility, and impact of your research: reporting guidelines and the EQUATOR Network. BMC 2010. Med (8): 24.

Table 1. Topic Groups and Their Chairs

Topic Groups	Chairs
1 Missing data	James Carpenter (UK), Katherine Lee (Australia)
2 Selection of variables and functional forms in multivariable analysis	Michal Abrahamowicz (Canada), Aris Perperoglou (UK), Willi Sauerbrei (Germany)
3 Initial data analysis	Marianne Huebner (USA) , Saskia le Cessie (the Netherlands), Werner Vach (Germany)
4 Measurement error and misclassification	Laurence Freedman (Israel), Victor Kipnis (USA)
5 Study design	Suzanne Cadarette (Canada), Mitchell Gail (USA)
6 Evaluating diagnostic tests and prediction models	Gary Collins (UK), Carl Moons (the Netherlands), Ewout Steyerberg (the Netherlands)
7 Causal inference	Els Goetghebeur (Belgium), Ingeborg Waernbaum (Sweden)
8 Survival analysis	Michal Abrahamowicz (Canada), Per Kragh Andersen (Denmark), Terry Therneau (USA)
9 High-dimensional data	Lisa McShane (USA), Joerg Rahnenfuehrer (Germany)

Table 2. Panels, Their Chairs and Co-chairs

Panels	Chairs and Co-chairs
Membership (MP)	James Carpenter (UK), Willi Sauerbrei (Germany)
Publications (PP)	Bianca De Stavola (UK) , Mitchell Gail (USA), Petra Macascill (Australia), Stephen Walter (Canada)
Website (WP)	Joerg Rahnenfuehrer (Germany), Willi Sauerbrei (Germany)
Glossary (GP)	Simon Day (UK) , Marianne Huebner (USA) , Jim Slattery (UK)
Simulation Studies (SP)	Michal Abrahamowicz (Canada), Harald Binder (Germany)
Contact Organizations (CP)	Douglas Altman (UK) , Willi Sauerbrei (Germany)
Literature Review (RP)	Gary Collins (UK), Carl Moons (the Netherlands)
Data Sets (DP)	Hermann Huss (Germany), Saskia Le Cessie (the Netherlands), Aris Perperoglou (UK)
Knowledge Translation (TP)	Suzanne Cadarette (Canada), Catherine Quantin (France)
Bibliography (BP)	To be determined

Mathematical Riddle

Let's see if you can solve this riddle – ***What is the largest number you can create by moving only two matches? The digits in this number should be similar in size. You are not allowed to change the place of digits, just to move two matches.***

** Please ignore the Hebrew! IBS does not reserve the rights for this riddle.*

Please send answers to *HaviM@gertner.health.gov.il*. The first five people to answer correctly will be mentioned in the next issue of the ***Biometric Bulletin***. Please also email interesting riddles to be published in future issues.

Region News

Australasian Region(AR)

Australasian Regional Conference

The next regional conference of the Australasian Region, titled "Biometrics by the Border", is to be held from 26 – 30 November in Kingscliff, NSW, at the Mantra on Salt Beach. Registration and abstract submission is now open: http://www.biometric2017.org.

The all-female line-up of keynote speakers celebrates achievements by women in the field of biometrics. We are excited to confirm that Elisabetta Carfagna (University of Bologna), Di Cook (Monash University), Rachel Fewster (University of Auckland), Sonja Greven (LM University Munich), Louise Ryan (University of Technology Sydney) and Jean Yang (University of Sydney) are sharing their latest insights in their respective fields. We will also be joined by IBS President Elizabeth Thompson.

Three pre-conference workshops are being offered: "Spatio-Temporal Statistics with R" presented by Chris Wikle and Petra Kuhnert (25 – 26 November), "Use of geospatial technology for agriculture & agri-environmental statistics" presented by Elisabetta Carfagna (26 November) and "Exploring data and models visually" presented by Di Cook (26 November).

The venue provides a range of accommodation types and budgets. It is adjacent to a great surf beach which is patrolled during that period. The Local Organising and Programme Committees are working hard to make this a conference you will appreciate attending from both a social and science perspective.

Further information is available on the conference website: http://www.biometric2017.org.

Mantra on Salt Beach (Gold Coast, Australia), the venue of "Biometrics by the Border".

Vanessa Cave