

STRATOS News

STRengthening Analytical Thinking for Observational Studies

Welcome to STRATOS News! This newsletter is brought to you by the Knowledge Translation Panel in an effort to connect and inform STRATOS members. Feedback is welcome — we aim to create a newsletter that is meaningful to you!

Knowledge Translation Panel

Co-chairs:

Suzanne Cadarette
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Members:

Lindsay Wong
Harbajan Chadha-Boreham



Welcome

Willi Sauerbrei, Freiburg, Germany

A very warm welcome from Freiburg to all members of the STRATOS initiative and to all other readers. This initiative started around 2010 with many discussions about model-building issues (discussions since the early 90's) with Martin Schumacher, Patrick Royston, Doug Altman, Hans van Houwelingen, Michal Abrahamowicz, Maria Blettner, Heiko Becher, James Carpenter, Lisa McShane and many others. However, the actual beginning was a result of some of my loose comments during the annual meeting of the Epidemiology Subcommittee of the International Society for Clinical Biostatistics (ISCB) on August 22, 2011 in Ottawa, Canada. The first item of the minutes, written by Vana Sypsa (VS, currently Vice-President of ISCB), entitled 'Guidance for the analysis of observational studies,' reads:

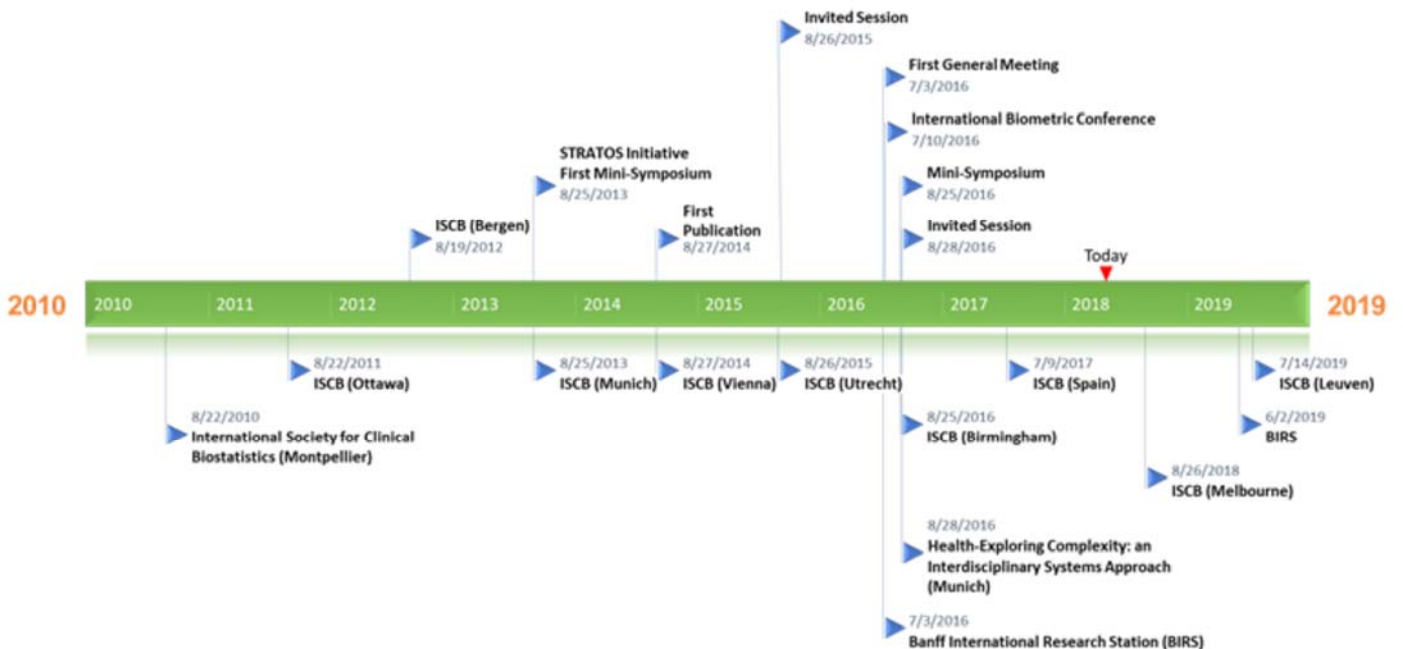
WS (Sauerbrei) proposed that one of the tasks the SC (Subcommittee) should pursue is the development of guidance for the analysis of observational studies. HCB (Chadha-Boreham) mentioned that this is also a particular problem in observational studies assessing therapeutic effects. WS has already approached other persons who are interested in this task. Several ideas have been discussed about how this could be pursued. One idea is to organise a workshop (perhaps by asking resources for the Epidemiology SC or in collaboration with the Education SC, as proposed by CQ (Quantin). Another possibility would be to organise it as a mini-symposium in one of the forthcoming ISCB conferences. GEE (Eide) noted that this would be difficult for the next year conference as there is already a mini-symposium organised on an epidemiological topic. The ISCB conference in Munich might be another possibility (WS will contact SPC [Scientific Program Committee] chair). In the meantime, preliminary work will be done through e-mails between the SC members so that we end up with a number of potential topics that could be discussed in Bergen with people who are interested in providing their expertise in this workshop/mini-symposium.

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Reading this summary in 2011, I had not imagined that this could have grown into such an impressive initiative after little more than six years. We established a Steering Group and at ISCB 2013 in Munich we had our first well-attended mini-symposium with talks from all seven (at that time) existing topic groups. The name STRengthening Analytical Thinking for Observational Studies (STRATOS) was selected for our international initiative and aims, concept, structure and the general approach of the STRATOS initiative were discussed. Our first paper (Sauerbrei et al, Statistics in Medicine 2014) summarizes this. From the beginning we were ‘intellectually rich, but cash poor!’ (see Glossary report by Simon Day) and it was difficult to professionally organize such an initiative with (by now) more than 80 members from 16 countries and four continents. Nevertheless, we succeeded in organizing further invited sessions and mini-symposia at meetings of the ISCB, International Biometric Society (IBS), some regions of IBS and others. A milestone was the first general STRATOS meeting at the Banff International Research Station (BIRS) in July 2016. Michal Abrahamowicz was the main applicant and organizer with his team from Montreal, and his experience helped us to apply for another BIRS meeting, to be held in June 2019 (see report by Michal Abrahamowicz). I and certainly many of you are very much looking forward to this meeting. In 2016, we started two new Topic Groups (TG): TG8 - Survival analysis and TG9 - High-dimensional data. While preparing for BIRS 2016 we realized the necessity of cross-cutting panels, to deal with issues such as common terminology (see Glossary Panel report by Simon Day), ‘rules’ for talks and papers on behalf of the STRATOS initiative (see Publication Panel report by Stephen Walter and Bianca de Stavola), or some ‘loose rules’ on reviewing the literature or conducting simulation studies (see Review Panel report by Gary Collins and Carl Moons and the Simulation Panel report by Anne-Laure Boulesteix). Simulation studies, or the extension to the more complex concept of ‘neutral comparison studies’, will become a key instrument to compare competing statistical methods and to create solid evidence to support our guidance documents.

Soon after the official launch of the STRATOS initiative in 2014, it became obvious that processes were needed for colleagues interested in becoming STRATOS members. The Steering Group realized that we needed to refine the structure of STRATOS to best facilitate the initiative’s aims. Recently we created three additional membership categories: Experienced Adjunct Members, Early Career Adjunct Members and Clinical Affiliates, whose roles are described further in the member-categories document (see Membership Panel report by James Carpenter and Willi Sauerbrei).



For an initiative like STRATOS it is important to cooperate with other societies, initiatives and projects. STRATOS has roots in reporting guidelines, for about a decade coordinated by the EQUATOR Network, but is an intellectual child of ISCB. Recently we started discussions about establishing an official partnership with ISCB and the EQUATOR Network. With an invited session at the International Biometric Conference 2016 we started cooperation with the International Biometric Society. Meanwhile, we had sessions at meetings of several regions of IBS and were invited to write a series of short STRATOS papers in the Biometric Bulletin. The introductory paper and a paper by TG1 (Missing data) have been already published, and the paper by TG4 (Measurement error and misclassification) will appear soon. From the beginning we discussed the importance of developing guidance for researchers with different levels of statistical training, skills and experience. Therefore, it is important to develop closer contacts with societies with different focus, aims and backgrounds, including societies regrouping potential end-users (e.g. epidemiologists and clinical researchers). In Germany we had invited sessions at meetings of such societies. Furthermore, the invitation from the European Medical Writers Association (EMWA) to present the STRATOS initiative in a special issue of their journal on observational studies clearly illustrates that the work we started is highly relevant for many stakeholders in research (analysts with different levels of statistical knowledge, reviewers, editors, teachers, students, journalists and funders). In the EMWA issue you will find several interesting articles (see summary by Marianne Huebner and Willi Sauerbri). Meanwhile all TGs have made substantial progress. The first papers and letters have appeared or are under review. TG7 (Causal inference) has created its own website and is giving courses about issues in causal inference and TGs 2 (Selection of variables and their functional form in multivariable analysis), 6 (Evaluating diagnostic tests and prediction models) and 7 have successfully applied for a joint meeting in Leiden (see TG reports and the report about planned meetings).



Big data, reproducible research and data sharing are some of the most important challenges for future research in health sciences. STRATOS deliberately decided not to have a 'Big Data' topic group, but instead to encourage all TGs to consider how their work relates to, can be motivated by, or adapted in order to respond to specific challenges induced by 'Big Data'. Furthermore, TG9 (High-dimensional data) is concerned with the specific analytical problems that arise with -omics data, where the number of variables is typically far greater than the number of study subjects.

STRATOS strongly supports reproducible research, as clearly stated in the general requirements for STRATOS papers. For levels 1 and 2 papers (see report from the Publications Panel) results need to be reproducible and papers should be Open Access. Data and code need to be made available. For level 3, papers should preferably be Open Access and results should ideally be reproducible. Obviously, to fulfill these criteria data sharing is an important pre-require for successful research. STRATOS and its Data Sets Panel welcome and support data sharing initiatives.

We need active members helping with the communication within the initiative and with the transfer of knowledge to a much broader audience. Our group in Freiburg developed a static website providing the most pertinent information. In addition, slides from nearly all STRATOS talks, some videos and the BIRS report are available. There are plans for substantial improvements of the website. This first newsletter is another milestone of our young initiative. Big thanks to the Knowledge Translation Panel!

Running such an initiative requires financial support, but it is outside the typical scope of research funding agencies and organizations to support a research collaboration addressing a wide range of areas with many aims. Recently, I was successful with an application to the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) to finance several projects related to methodological issues in TG2. However, the DFG does not support work on a glossary or cover salaries and necessary equipment to create a dynamic and informative website according to nowadays technology. Identifying funding sources is one of the next important steps for the STRATOS initiative.

Membership

Beside regular members the initiative has three additional membership categories. Subject to appropriate contributions, members from each of these categories may also become co-authors of relevant STRATOS publications.

Experienced Adjunct Members

Experienced researchers who would like to occasionally contribute to specific STRATOS activities, but do not have the time commitment needed for regular Topic Group or Panel membership.

Description: Propose ideas to improve current and future work, engagement in reviewing STRATOS papers, providing feedback in TGs or Panels, but with less of a time commitment than would be expected for regular membership.

Early Career Adjunct Members

Researchers at earlier stages of their careers who are willing to participate in specific TG and Panel activities

Description: These are less experienced researchers, with statistical expertise and interests in the area of a specific TG or Panel, who indicated interest in STRATOS membership, but do not have the experience required to become full members of TGs or Panels. Engagement, at the discretion of TG and Panel Chairs, would be expected for example in literature reviews, Glossary Panel, simulation studies, or reviewing STRATOS papers.

Clinical Affiliates

Clinicians engaged in research, with interests and practical experience with statistical methodology relevant for at least one particular TG or Panel, who are willing to provide feedback and participate in discussions about strategy and direction to make sure STRATOS developments are accessible to a larger audience.

Description: These are experienced clinicians, with good understanding of applied statistics, who are willing to aid in panel issues and the development of level 1 and 2 guidance by engaging in discussions about directions, presentations, internal reviews and other tasks relevant for the initiative.

Spread the word, join STRATOS! Please send the [completed application form](#) and a two page CV including a list of max. 10 publications from the last 10 years via email to:

contact@stratos-initiative.org



Publications

1. Sauerbrei W, Abrahamowicz M, Altman DG, le Cessie S and Carpenter J on behalf of STRATOS initiative. STRengthening Analytical Thinking for Observational Studies: The STRATOS initiative. *Statist Med.* 2014; 33: 5413-5432. DOI: 10.1002/sim.626.
2. Sauerbrei W, Abrahamowicz M, le Cessie S for the STRATOS initiative. The STRATOS initiative - Motivation, Mission, Structure and Main Aims. *ISCB News* 2016; 62: 6-7.
3. Huebner M, Vach W, le Cessie S. A systematic approach to initial data analysis is good research practice. *J Thoracic Cardiovas S.* 2016; 151(1): 25-27.

Series of papers for the Biometric Bulletin:

4. Sauerbrei W, Huebner M, Collins GS, Lee K, Freedman L, Gail M, Goetghebeur E, Rahnenfuehrer J, Abrahamowicz M on behalf of the STRATOS initiative. STRATOS initiative – Guidance for designing and analyzing observational studies. *Biometric Bulletin* 2017; 34(3): 18-20. www.biometricsociety.org/vol-34-no-3.
5. Carpenter J and Lee KJ on behalf of STRATOS TG1. STRengthening Analytical Thinking for Observational Studies (STRATOS): Introducing the Missing Data topic group (TG1). *Biometric Bulletin* 2017; 34 (4): 11-13. www.biometricsociety.org/vol-34-no-4.
6. Freedman L and Kipnis V on behalf of STRATOS TG4. STRengthening Analytic Thinking for Observational Studies (STRATOS): Introducing the Measurement Error and Misclassification Topic Group (TG4). *Biometric Bulletin* 2018; 35 (1).



7. Sauerbrei W, Collins GS, Huebner M, Walter SD, Cadarette SM, Abrahamowicz M on behalf of the STRATOS initiative. Guidance for designing and analyzing observational studies: The STRengthening Analytical Thinking for Observational Studies(STRATOS) initiative. *Medical Writing* 2017;26(3):17-21. journal.emwa.org/observational-studies.
 - European Medical Writers Association published a short introduction of the STRATOS initiative in a special issue about observational studies (see also the report by Marianne Huebner and Willi Sauerbrei).
8. Anne-Laure Boulesteix A, Binder H, Abrahamowicz M, Sauerbrei W for the Simulation Panel of the STRATOS Initiative. On the necessity and design of studies comparing statistical methods. *Biometrical Journal* 2018; 60: 216-218.
9. Huebner M, le Cessie S, Schmidt CO, Vach W on behalf of the Topic Group 'Initial Data Analysis' of the STRATOS Initiative. A Contemporary Conceptual Framework for Initial Data Analysis; *Observational Studies* 4 (2018) 171-192.

Addressing challenges in observational studies

Marianne Huebner (East Lansing, USA) & Willi Sauerbrei (Freiburg, Germany)

A paper introducing the STRATOS initiative [1] to non-statisticians was published in the special issue on Observations and Observational Studies of Medical Writing, the official journal of the European Medical Writers Association. Here is a brief summary of some topics discussed in other articles in the same edition of this journal.

There are regulatory differences between countries regarding obtaining ethics approval for observational studies [2]. ClinicalTrials.gov allows the registration of observational studies and provides specific data elements to be filled in for registration. FDA has made decisions on the basis of results from observational studies. The recommendation is to obtain ethics approval to prevent bad research practices. Some journals instruct authors on statements to be included in manuscripts [2, Table 2].

Statistical terms can be used inconsistently, do not have a clear meaning, or are difficult to understand, such as risks, odds, or hazards. In correctly interpreting the results from an observational study it is helpful to have clear definition and understanding of these terms [3]. The Glossary Panel in the STRATOS initiative is making an effort in that direction.

There are different types of observational studies depending on the data collections such as cases or series, surveys, genomics, patient registry, imaging and markers, and others. Critical information about the data selection and analysis methods that allow for careful interpretation of the results is often lacking [4]. The STROBE checklist (www.strobe-statement.org) is a guideline for reporting results of observational studies. Several guidelines are under development to extend this checklist, as summarized on the EQUATOR Network website (www.equator-network.org/library/reporting-guidelines-under-development).

Patient registries are observational data based on clinical practice and may have different purposes, effectiveness of interventions, safety, and quality of care [5]. According to the Agency for Healthcare Research and Quality, "A patient registry is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes." The design and analysis of studies based on registry data must consider selection bias and confounding, and there is a need for sophisticated statistical methodologies.

References:

1. Sauerbrei W, Collins GS, Huebner M, Walter SD, Cadarette SM, Abrahamowicz M. Guidance for the design and analysis of observational studies (STRATOS) initiative. *Medical Writing* 2017; 26(3): 29-34, available on the STRATOS website.
2. Singh N. Registration and ethics: committee approval for observational studies. *Medical Writing* 2017; 26(3): 29-34.
3. Lang T. Odd cases and risky cohorts: measures of risk and association in observational studies. *Medical Writing* 2017; 26(3): 12-16.
4. Rossi A, Benci C, and Leventhal PS. Guidelines for disclosing the results from observational trials. *Medical Writing* 2017; 26(3): 22-28.
5. Koltowska-Haeggstroem M. RCTs. Can the treatment work? Patient registries: Does the treatment work? *Medical Writing* 2017; 26(3): 6-11.

2017 Year in Review

Sep 17 – 21: [Jahrestagung GMDs](#), Oldenburg, Germany

STRATOS Session 1

Willi Sauerbrei— *'Introduction of the STRATOS initiative and its main aims'*
 Peggy Sekula— *'Prognostic studies and the need for guidance'*
 Carsten Oliver Schmidt on behalf of TG3— *'A Contemporary Conceptual Framework for Initial Data Analysis'*
 Veronika Deffner on behalf of TG4— *'TG4 on measurement error and misclassification'*



STRATOS Session 2 (organised by TG9: design and analysis of high dimensional data)

Axel Benner on behalf of TG9— *'Simulating High-Dimensional Molecular Data'*
 Harald Binder & Jörg Rahnenführer— *'Discussion on future challenges and plans of the initiative and on possibilities to join or cooperate with STRATOS.'*

Sep 5 – 8: [Gemeinsame Jahrestagung DGEpi, DGMS und DGSMP](#), Lübeck, Germany

Willi Sauerbrei— *'The STRATOS initiative, illustrated by issues in Topic group 2: selection of variables and their functional form'*

Aug 28 – Sep 1: [CEN ISBS joint conference Biometrics & Biopharmaceutical Statistics](#), Vienna, Austria

STRATOS Session 1. Chair: Michal Abrahamowicz

Willi Sauerbrei— *'Motivation, Mission, Structure and Main Aims of the STRATOS Initiative'*
 Matthias Schmid on behalf of TG2— *'Spline Regression Modeling Using R - Methods and First Results'*
 Pamela Shaw on behalf of TG4— *'Statistical methods to Address Measurement Error in Observational Studies: Current Practice and Opportunities for Improvement'*

STRATOS Session 2. Chair: Willi Sauerbrei

Doug Altman on behalf of TG5— *'Issues in popular designs for observational studies'*
 Peggy Sekula on behalf of TG5— *'Prognostic studies and the need for guidance'*
 Jörg Rahnenführer on behalf of TG9— *'Analysis of high-dimensional data: Guidance or (best) practice?'*
 General discussion on future challenges and possibilities to join STRATOS.

Jul 9 – 13: [ISCB](#), Vigo, Spain

For the first time, STRATOS was named as a scientific topic to encourage the scientific community to submit abstracts related to STRATOS topics. The following two STRATOS sessions were organized. Not all talks were given on behalf of the STRATOS initiative.

STRATOS Session 1:

Willi Sauerbrei on behalf of the STRATOS Initiative— *'On 'state-of-the-art' for selection of variables and functional forms in multivariable analysis'*
 Christen Gray, London School of Hygiene and Tropical Medicine, London, UK— *'Accounting for complex measurement error in fractional polynomial models, with an application to alcohol and mortality'*
 Aris Perperoglou on behalf of TG2 of the STRATOS initiative— *'A comparison of spline methods in R for building explanatory models'*

STRATOS Session 2:

Philip Clare, UNSW Australia, Australia— *'Comparison of methods for adjusting for time-varying confounding'*
 Rebecca Whittle, Keele University, UK— *'Measurement error and timing of predictor values used in prediction model research: a systematic review of current practice and reporting'*
 Camila Olarte Parra, Ghent University, Belgium— *'Is kidney transplantation best preceded by dialysis? On avoiding potential biases through G-estimation'*

May 8 – 12: [EMR-IBS and Italian Region conference](#), Thessaloniki, Greece

STRATOS session

Georg Heinze on behalf of TG2— *'Why many researchers misuse variable selection and how to prevent this'*
 Michal Abrahamowicz on behalf of TG8— *'STRATOS and flexible modeling of time-dependent covariates in time-to-event analyses'*
 Pamela Shaw on behalf of TG4— *'Measurement Error in Nutritional Epidemiology: Impact, Current Practice for Analysis, and Opportunities for Improvement'*
 Victor Kipnis on behalf of TG4— *'A new longitudinal time-varying measurement error model with application to physical activity assessment instruments in a large biomarker validation study'*

2nd STRATOS Workshop at the Banff International Research Station (Canada), June 2-7, 2019

Michal Abrahamowicz (Montréal, Canada)

Following the very successful and productive 1st STRATOS workshop, in July 2016, at the Banff International Research Station (BIRS), the BIRS Scientific Review Committee has accepted the STRATOS application for the 2nd workshop, to be held in Banff, in the Canadian Rocky Mountains, on June 2-7, 2019 (www.birs.ca). The organizers are Michal Abrahamowicz (contact organizer), Richard Cook, Marianne Huebner and Willi Sauerbrei, with James Carpenter and Els Goetghebeur as additional members of the Scientific Program Committee.



The overall objectives of the 2019 workshop “Next Stages Toward a Comprehensive, Integrated Framework for Advanced Statistical Analyses of Observational Studies” will be to develop, accelerate and consolidate the work of the members of STRATOS initiative’s Topic Groups and Panels. In particular, building on recommendations that will be proposed by each Topic Group, to address the main analytical challenges within their area of expertise, we will continue drafting guidance documents and designing comprehensive strategies to deal simultaneously with several problems likely to be encountered in real-life empirical studies. The workshop will facilitate such inter-disciplinary discussions and developments.

The 4 general inter-related objectives of the workshop are:

- 1) to provide an overview of the methods, related to the area of expertise of individual Topic Groups, applied in the current empirical studies and identify the priorities for improving the methodological quality of such studies;
- 2) to identify methodological challenges, within the area of expertise of each of the 9 Topic Groups, that require further validation or comparison of new or existing methods, and outline the analytical work or simulation studies necessary to provide reliable evidence supporting specific approaches and demonstrating the limitations of other methods, in the spirit of ‘neutral comparison studies’ (onlinelibrary.wiley.com/doi/10.1002/bimj.201700129/);
- 3) To set the definitive objectives, design, and methods of the comprehensive series of simulations that will approximate the complexity of large real-life empirical observational studies and investigate issues at the cross-roads of the interests of various Topic Groups;
- 4) To develop the uniform format, criteria, and general content for the integrated STRATOS-based guidance documents.

STRATOS Topic Groups and Panels will present drafts of their guidance, related to fundamental issues and relying on recent methodological developments in their respective areas. Debating these will lead to evidence supported decisions and, on the other hand, will help focus the meeting on novel research projects aiming at the development and validation of new multi-stage methods, necessary to simultaneously address several frequently encountered analytical challenges.

BIRS workshops can accommodate up to 42 participants (including 4-6 research trainees) and 3 observers. As STRATOS membership has grown to >80 members, it will be impossible to invite all members. Therefore, the final decisions for inviting STRATOS members to attend the 2019 BIRS workshop will be taken by the Chairs of Topic Groups and Panels, based on individual researchers’ contributions to the relevant STRATOS activities.

We look forward to another very productive and enjoyable meeting in Banff!

Simulation Studies Panel

Anne-Laure Boulesteix (Munich, Germany) on behalf of the Simulation Studies Panel

To investigate properties, to compare and validate alternative statistical approaches and to create evidence for guidance, simulation studies play a key role. Many of us have much experience designing and analyzing simulation studies, but we all know about the difficulties and problems they pose, and in general there is often criticism of the quality and usefulness of such studies. Anne-Laure Boulesteix, Harald Binder, Michal Abrahamowicz and Willi Sauerbrei have recently published a provocative letter entitled 'On the necessity and design of studies comparing statistical methods' in the *Biometrical Journal* (2018, 60:216-218) for the Simulation Studies Panel of the STRATOS Initiative. Here is a short summary including issues related to simulations.

"In data analysis sciences in general and in biometrical research particularly, there are strong incentives for presenting work that entails new methods [...]. Such a research paradigm is not favorable for studies that aim at meaningfully comparing alternative existing methods or, more generally, studies assessing the behavior and properties of existing methods. [...] It is well-known that studies comparing a suggested new method to existing methods may be (strongly) biased in favor of the new method. This is a consequence of various factors starting with the authors' better expertise on the new method compared to the competing methods. Another factor is the combination of publication pressure ("publish or perish") and publication bias – in the sense that a new method performing worse than existing ones has (severe) difficulties to get published. [...] In contrast, neutral comparison studies are dedicated to the comparison itself: they do not aim to demonstrate the superiority of a particular method and are thus not designed in a way that may increase the probability to observe incorrectly this superiority. Furthermore, they involve authors who are, as a collective, approximately equally competent on all considered methods. [...] Yet, in practice, such neutral comparison studies may be very time consuming and difficult to both organize and perform. [...]"

Let us consider this situation in light of a keen analogy with clinical research: imagine that medical researchers spend most of/all their time developing new therapies that are not evaluated in clinical trials. Imagine that performing clinical trials for comparison is considered non-innovative research, not worth funding and not worth publishing in high-ranking journals. Imagine that nobody cares about the way clinical trials are performed, their design, their biases, their reliability, the interpretation of their results, etc. This clearly unacceptable situation would be somewhat similar to the (partial) lack of interest of the statistical research community in systematic (simulation-based) comparisons of existing statistical methods.



Moreover, it is not clear how these comparison studies should be performed and reported: more (meta-) research is needed. [...] "What are typical sources of potential biases and how can they be avoided? How can the results be interpreted without the tendency for over-interpretation? Which mixture of simulated and real data should be used? How should real data be selected? How should simulated data be generated in a realistic way inspired from real datasets? What parameters and assumptions should be varied across the simulated scenarios? What range of sample sizes should be assessed? How can we assess the practical relevance of simulation results, which depends on the real-life plausibility of the simulation scenarios? How can an acceptable neutrality of the authors team be achieved and how can non-neutrality (the analogon of "conflicts of interest" in clinical research) be disclosed? Which "competing methods" should be considered? [...]"

In this context, to improve comparison studies of statistical methods and their reproducibility we consider it desirable to (i) reinforce the status of neutral comparison studies and studies evaluating the behaviors of existing methods in the scientific community with the aim to create incentives to perform such studies; (ii) develop research activities dedicated to what we could call "comparology", i.e. research on how to reliably assess statistical methods - in analogy to the active research field devoted to clinical trial methodology."

The aim of the simulation study panel is to foster and develop such research activities dedicated to "comparology", whereby simulations play an important role.

Knowledge Translation Panel

Suzanne Cadarette (Toronto, Canada) on behalf of the Knowledge Translation Panel

The Knowledge Translation Panel aims to spread the word about STRATOS. Creating a brand for the STRATOS Initiative was our first step towards this goal. Many thanks to everyone who participated in our STRATOS Initiative Logo Contest! The result is the logo you see on this newsletter as well as the STRATOS website. This inaugural STRATOS newsletter is another major milestone to connect STRATOS members and celebrate our achievements!



Thanks to everyone who helped make this happen!

Glossary Panel

Simon Day (London, UK) on behalf of the Glossary Panel

Unfortunately, we have not made a lot of progress...but we are trying! We do have a potential “starting point” for a glossary (Simon Day’s book *Dictionary for Clinical Trials*, published by Wiley 1999 and 2007). We have stripped out from that all the terms not relevant to STRATOS and included a few additional ones that are, but it is still very much an internal document: not ideal, and potentially quite limited in scope. As an alternative approach, we are trying to contact (and partner with) the American Medical Association. They have a Glossary of Statistical Terms (www.amamanualofstyle.com/view/10.1093/jama/9780195176339.001.0001/med-9780195176339-div1-215) and rather than duplicate effort, it would have been good if we could contribute to that and, at the same time, use what they have already developed. It would also give STRATOS some additional visibility. Unfortunately, the copyright for the glossary seems to be owned by Oxford University Press and they were not prepared to open it up without some financial remuneration. STRATOS, as we all know, is intellectually rich, but cash poor!

Meanwhile, one of our tasks is to review manuscripts being submitted for publication under the STRATOS label. The review is for consistency of terminology (both within-papers and across-papers) – we are not trying to offer a scientific review since the Topic Group members typically will be far more expert in the subject matter. But sometimes a fresh pair of eyes can be helpful to even the best authors. So far this exercise has proved useful in contributing new terms to the glossary, so a service to us, just as much as a service to the authors.

Literature Review Panel

Gary Collins (Oxford, UK) on behalf of the Literature Review Panel

Our scope is to provide guidance to STRATOS groups for conducting literature reviews of statistical methodology of observational research. All Topic Groups are expected to work on a review of statistical methods used in their field. Such reviews may assess both (a) what and how specific methods, relevant for a given TG, are used in recent ‘applied’ studies; or (b) what relevant guidance or review documents have been recently published. The Literature Review Panel has derived a general structure and recommendations concerning many issues (e.g., protocol development and registration, data extraction, selection of suitable journals, search strategy and data management). Aiming for a uniform approach for high quality, reviews coordinated and (partly) harmonized across Topic Groups will be helpful. As methodological issues from several Topic Groups are relevant in many analyses, it is expected that corresponding topic groups collaborate. This Panel will be closely linked to the glossary panel, to ensure a consistent use of terminology.

Publications Panel



Bianca De Stavola (London, UK) & Stephen Walter (Hamilton, Canada)
on behalf of the Publications Panel

As described elsewhere in detail (see Welcome, by W. Sauerbrei), the STRATOS initiative is composed of nine “topic groups” (TGs) that focus on pressing methodological challenges currently posed by the design and analysis of observational studies. Its goals are:

- a) to identify guiding principles and state-of-the-art tools to address them; and
- b) to make them accessible to applied researchers by sharing their findings.

Given the broad spectrum of statistical expertise among those involved in the design and analysis of observational studies, different levels of outputs are planned, including publications in scientific journals, web-based resources, and short courses. These levels are broadly defined as level 1, 2 and 3, with an increasing gradient in methodological expertise required to appreciate their content.

To co-ordinate and standardize the work of the TGs, ten cross-cutting Panels have been constituted. The merit of the Publication Panel (PP) is to outline guidance for STRATOS publications and presentations and to facilitate their adoption. For this reason, authors of TG- or panel-related publications need to submit their work to the PP, to receive the relevant support in meeting STRATOS standards. Its membership is meant to be extensive and representative of a variety of fields and expertise and currently includes: Stephen Walter and Bianca De Stavola (Chairs), Mitchell Gail and Petra Macaskill (Co-chairs), Willi Sauerbrei, Simon Day for the Glossary Panel, Suzanne Cadarette for the Knowledge Translation Panel, and contributors of TGs not already represented by these members (Marianne Huebner for TG3, Pamela Shaw for TG4, Jeremy Taylor for TG8 and Joerg Rahnenfuehrer for TG9).

The Publication Panel’s main principles for evaluating and then endorsing a publication are:

1. The work is compatible with the STRATOS objectives and target audiences. More specifically:
 - **Level 2** papers should provide a very balanced summary of the available methods, outlining their advantages and disadvantages, and the presentation is supported by evidence from the methodology literature and simulation studies, as well as by practical examples. It is crucial that what is reported reflects consensus (or near-consensus) among methodologists (in the broadest sense, not just STRATOS members) regarding validity and best practice.

As there are several areas where it is important to expand what is presented in Level 2 papers, both to eradicate major errors and to report on current developments, two additional levels of publications are endorsed:

- **Level 1** papers will aim to eradicate errors. These will be illustrated by real-life and, if useful, simulated examples and accompanied by recommendations on the readily available, user-friendly methods that can help in identifying and/or avoiding major problems and biases, while not requiring in-depth understanding of the method. Accessibility of the software and ease of interpretation of the results will be important criteria for level 1 recommendations, implying that some more powerful/efficient, yet more complex methods, recommended in level 2 documents, may not be recommended at level 1.
- **Level 3** papers will be targeting the more experienced data analysts and researchers, and aim to provide a balanced assessment of novel methodological developments, and, if relevant, any related software. We expect recommendations to be nuanced. Indeed, one important output of the level 3 guidance will be to identify the need for further research on the evaluation and development of various methods.

2. As far as possible, papers should ideally be Open Access, results should be reproducible, with data and software made available in conjunction with the publication.
3. There should ideally also be consistency of terminology across STRATOS publications.
4. The authors should be representative of the relevant TG (or panel) and include their Chairs.

Not surprisingly, translating these general rules into practice is not straightforward. So far, the Publication Panel has received submissions from four TGs and one panel and each submission has involved very interesting discussions -within the panel and with the authors- about how best to meet those guiding principles. The outcome in each case has been positive for all those involved, and several papers have been submitted now under the STRATOS umbrella. As we expect more submissions, we also expect more discussion, and this can only be good for our discipline. We look forward to reading more!

Upcoming Meetings, 2018-2019

Jul 8-13, 2018: IBC, Barcelona, Spain. www.biometricsociety.org/meetings-events/ibcs/

- STRATOS session was not selected but several talks were submitted and a special session is in discussion

Aug 27-30: ISCB, Melbourne, Australia. iscbasc2018.com

- Invited session organized by Lee and Sauerbrei. Presenters: Abrahamowicz, Kipnis and Therneau

Sep 3-6, 2018: RSS, Cardiff, Wales.

- Invited session organized by Perperoglou. Presenters: Keogh, Perperoglou, Sauerbrei

Dec 17-20, 2018: EMR-IBS, Jerusalem, Israel. www.emr2018.com

- Invited session suggested by Havi Murad, Editor of Biometric Bulletin Organized by Abrahamowicz and Sauerbrei. Presenters: Freedman, Kipnis and Sauerbrei

Jun 2-7, 2019: BIRS, Banff, Canada

- 2nd STRATOS Workshop (see report by Michal Abrahamowicz)

TG meetings:

Mar 20-22, 2018: Dortmund, Germany

- Supported by a large research project of the Department of Statistics, TU Dortmund 'High-dimensional data: Design and Analysis', Five talks from TG9 members in the seminar series of this research project

Jun 18-19, 2018: Hamburg, Germany

- TG3 meeting

Sep 17-21, 2018: Leiden, Netherlands

- TG2, TG6 and TG7— joint meeting in Leiden, Netherlands



Topic Group Updates

TG 1: Missing Data

James Carpenter (London, UK) & Katherine Lee (Melbourne, Australia) on behalf of the Topic Group 1

The aim of TG1 is to provide guidance on how to handle missing data and reporting of such analyses. This will be achieved through a series of linked papers. The first paper will compare three popular methods for handling missing data in a social science setting: complete cases, weighting and multiple imputation. The second paper aims to provide and illustrate a practical framework for the analysis of partially observed data and subsequent reporting. The third paper will discuss both theoretically and with examples, the utility of key approaches to the analysis of partially observed data, in particular: full Bayesian analysis, multiple imputation, inverse probability weighting, doubly robust estimation, direct maximum likelihood and the EM algorithm. All of these papers will include worked examples based on a publically available dataset along with example code, with the first 2 papers in a fairly advanced draft.



TG 2: Selection of Variables and Functional Forms in Multivariable Analysis

Aris Perperoglou (Essex, UK) on behalf of Topic Group 2

The aim of TG2 is to provide accessible and accurate guidance in issues concerning the selection of variables and the determination of functional form for continuous variables in multivariable analysis.

Five presentations were made on behalf of TG2 in 2017: At the IBS-EMR meeting in Thessaloniki, Greece, Georg Heinze presented a talk entitled '*Why many researchers misuse variable selection and how to prevent this*', Willi Sauerbrei presented '*On 'state-of-the-art' for selection of variables and functional forms in multivariable analysis*' and Aris Perperoglou presented '*A comparison of spline methods in R for building explanatory models*' in ISCB Conference in Vigo, Spain. Willi Sauerbrei talked on '*Motivation, Mission, Structure and Main Aims of the STRATOS Initiative*' and Michal Abrahamowicz presented '*Spline Regression Modeling Using R - Methods and First Results*' in CEN-ISBS Conference on Biometrics and Biopharmaceutical Statistics in Vienna, Austria. In addition, Willi Sauerbrei had the closing talk at the '*Gemeinsame Jahrestagung DGEpi, DGMS, DGSMP*' in Lübeck, Germany. His title was '*The STRATOS initiative, illustrated by issues in Topic group 2: selection of variables and their functional form*'.

The group has submitted one paper to Statistics in Medicine "A review of spline procedures in R" that targets level 2 audience with the aim to provide an overview of the most widely used spline-based techniques and their implementation in R, as well as an introduction to spline modelling and an overview of popular functions. All members of the group are contributing towards a second manuscript "On the state-of-the-art for selection of variables and functional forms in multivariable analysis", to be submitted within the next three months. The paper will present major challenges, highlight issues in variable selection and their functional form and be used a point of reference for work that needs to be done within the group.

The proposal for a TG2 related conference session in the next RSS meeting (September 2018, Cardiff) was accepted. Together with TGs 6 and 7 we will have a workshop in Leiden, September 17-21.

TG 3: Initial Data Analysis

Marianne Huebner (East Lansing, USA) on behalf of Topic Group 3

Our scope involves initial data analysis for observational studies in health care. While scientists perform IDA as part of observational studies, there has not been a consensus on the elements of IDA. Obstacles to a systematic approach can be lack of resources, time constraints, or organizational barriers. IDA needs to be recognized as an important and genuine element of the research process, since an informal or unstructured approach may have a large and non-transparent impact on results and conclusions presented in publications.

We have developed a systematic framework for IDA from the perspective of a traditional empirical study with six steps: (1) Metadata setup, (2) Data cleaning to identify and correct data errors, (3) Data screening that consists of understanding the properties of the data, (4) Initial data reporting to inform potential collaborators about all relevant insights from the previous IDA steps needed to properly conduct the intended analyses, (5) Refining and updating the analysis plan (based on findings from the previous IDA steps), (6) Reporting of IDA in research papers. Basic principles and illustrative examples are included in the paper.

Aims for the coming year are: (1) perform a literature review on reporting of IDA, (2) provide more detailed guidance for the separate IDA steps, (3) provide detailed worked-out examples in which the different IDA steps are applied.

TG 4: Measurement Error and Misclassification

Laurence Freedman (Tel Hashomer, Israel) on behalf of Topic Group 4

The aim of TG4 is to increase awareness of measurement error issues in observational epidemiology, and provide clear and accessible guidance on how to deal with such issues.

The group currently has two papers that are in an advanced stage of development. The first is a survey of the awareness of measurement error in four subject areas of epidemiology. The lead author is Pamela Shaw. This paper is currently submitted to a journal and is under review. The second is a guidance paper for biostatisticians on measurement error and misclassification of variables in observational epidemiology. The lead author is Laurence Freedman. The first eight sections have been completed and a final ninth section is being drafted. We anticipate a completed draft by the end of 2017.

Two more papers are at an earlier stage of development. The first is a tutorial and guidance paper for nutritional epidemiologists on dietary measurement error. The lead author is Ruth Keogh. Three sections have been completed and the anticipated time to first draft is approximately 6 months. The second is a case-study paper on how to do measurement error correction in practice with real-life examples. The lead authors are Ruth Keogh and Pamela Shaw. Work is just now beginning on this paper.

Several presentations were made on behalf of STRATOS TG4 in 2017. Victor Kipnis and Pamela Shaw presented at the bi-annual conference of the Eastern Mediterranean Region (Greece, May 2017); Ruth Keogh contributed to a pre-conference course at the annual meeting of the Netherlands Epidemiological Society (Antwerp, June 2017); Ruth Keogh and Pamela Shaw taught a half-day course at the Central European Network of the International Biometrics Society and also presented lectures at the conference (Austria, August 2017); and Veronika Deffner presented at the German Association for Medical Informatics (GMDS) (Oldenburg, Germany, September 2017).



TG 5: Study Designs

Suzanne Cadarette (Toronto, Canada) & Mitchell Gail (Rockville, USA) on behalf of Topic Group 5

The aim of TG5 is to provide accessible and accurate guidance in the design of observational studies.

Three presentations were made on behalf of STRATOS TG5 in 2017: Doug Altman presented on *Issues in Popular Designs for Observational Studies* at the Central European Network - International Biometric Society (CEN-ISBS) Joint Conference on Biometrics and Biopharmaceutical Statistics in August; and Peggy Sekula presented on the *Design of Observational Studies and the Need for Guidance using Prognostic Studies as an Example* at CEN-ISBS in August, and the German Association for Medical Informatics, Biometry and Epidemiology (GMDS) in September.

TG5 “paper 1” targets the level 1 audience and focuses on design options for detecting an association between exposure on disease outcome. A condensed draft is under review by TG5 members, and several follow-on papers (e.g., threats to validity in study design) and topics for other papers (e.g., prognostic studies) are under consideration.

TG5 members are also providing insight with early comments on draft guidance material prepared by the Self-Controlled study design Working Group (SCWiG) funded by the International Society for Pharmacoepidemiology.



TG 6: Evaluating Diagnostic Tests and Prediction Models

Gary Collins (Oxford, UK) on behalf of Topic Group 6

In medicine, numerous decisions are made by care providers, often in shared decision making, on the basis of an estimated probability that a specific disease or condition is present (diagnostic setting) or a specific event will occur in the future (prognostic setting) in an individual.

The aim of TG6 is to raise awareness of issues in the assessment of performance of diagnostic tests and prediction models, and to provide clear guidance on how to address such issues.

Our aims over the coming year are (1) to perform a literature review of the clinical literature to evaluate the methods and reporting of how prediction model calibration is assessed, (2) to perform a literature review of the available methods to evaluate model calibration, and to highlight their strengths and weaknesses, and (3) to perform an empirical comparison of the available calibration methods. The third paper will include worked examples based on a publicly available dataset along with example code.

A workshop (‘The Future of Statistical Modelling in Medical Data’) will take place in Leiden (The Netherlands) alongside TG2 and TG7 in September 2018.

TG 7: Causal Inference

Els Goetghebeur (Ghent, Belgium) & Ingeborg Waernbaum (Uppsala, Sweden)

on behalf of Topic Group 7

The topic group has had meetings and activities according to the following:

We had meetings and worked on an article during the spring of 2017 in Umeå January 19-22, in Leiden 28/2 and in Ghent 1-4/3. During these meetings we also constructed a didactical simulation tool of observed and potential treatments with joint potential outcomes to highlight and illustrate differences between various causal estimands and their estimated values. The simulation tool as well as course material can be found on our website, built during the spring of 2017: ofcaus.org.

On June 9, 2017 we organized and taught a pre-conference course at the 38th Annual conference of ISCB 2017 in Vigo, “Causal questions and principled answers: a guide through the landscape for practising statisticians”. We are also giving the short course in Montreal at the annual meeting of the Statistical Society of Canada June 3, 2018.

An extension of the short course was co-taught in Paris with Raphael Porcher, on January, 15-19, 2018 for the master program of comparative effectiveness research, CER, at the University of Paris Descartes.

TG 8: Survival Analysis

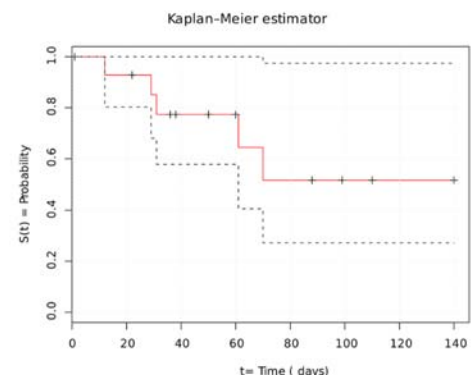
Michal Abrahamowicz (Montreal, Canada) on behalf of Topic Group 8

The over-arching objective of TG8 is to provide accessible and accurate guidance about specific analytical challenges encountered in the analysis of observational (prospective or retrospective) studies with outcome defined as (censored) time-to-event, including competing risks and multi-state modelling. We will aim at explaining the main concepts, and provide practical recommendations regarding the choice of methods that address specific challenges and statistical software that implements these methods. We will illustrate selected analytical issues and applications of the proposed methods with examples involving real-life and/or simulated data.

In June 2017, the first in-person meeting, in Copenhagen, was attended by 6 (out of then 8) TG8 members. We outlined the content of the two first TG8 manuscripts, both targeting ‘level 2’ of statistical expertise, aimed at an applied biostatistical journal, e.g. *Statistics in Medicine* or *SMMR*. The first paper will focus on the analysis of time to a single event and will cover general issues in modelling survival data, including time-varying covariates and time-dependent effects. Sources of some common errors will be explained and the methods to avoid such errors will be outlined. Alternative ways to provide more meaningful summaries of the results of hazard-based analyses will be proposed. We will also attempt to address some recent, highly influential commentaries by causal inference experts who question the current trend to rely heavily on hazard-based models. The second paper will focus on more complex analyses, involving competing risks and/or multi-state modelling of transitions between multiple (consecutive or mutually exclusive) states.

In 2017, Michal Abrahamowicz presented, on behalf of TG8, the talk: ‘STRATOS and flexible modelling of time-dependent covariates in time-to-event analyses’ at the Invited STRATOS session at the 9th EMR-IBS conference, in Thessaloniki, Greece.

In 2018, Terry Therneau will speak on behalf of TG8 at the Invited STRATOS session of the ISCB conference in Melbourne, Australia, and will offer a full-day pre-conference course on multi-state modelling.



TG 9: High-dimensional data

Lisa McShane (Bethesda, USA) & Jörg Rahnenfuehrer (Dortmund, Germany) on behalf of Topic Group 9

The aim of TG9 is to provide guidance regarding the multitude of opportunities and pitfalls inherent in the analysis of high-dimensional biological and medical data. Illustrative examples representing rich high-dimensional data sets, presented together with in-depth evaluation and discussion of various statistical and computational approaches, aim to support specific recommendations for best practices. Subtopics receiving special emphasis include, among others, data pre-processing, exploratory data analysis, multiple testing, prediction modeling, and data simulation methods.

The group will come together for the 1st Workshop of TG9 with the title “High-dimensional data: Design and Analysis” at TU Dortmund University, March 20-23, 2018. In the workshop, main topics will be the preparation of a draft for an overview paper of TG9 discussing issues for all subtopics, the identification of illustrative examples, and progress and future plans regarding data simulation methods for high-dimensional data. Overview presentations will be delivered within the seminar series of the Collaborative Research Center (CRC) SFB 876 at TU Dortmund University by Willi Sauerbrei, Riccardo De Bin, Tomasz Burzykowski and Lisa McShane.

In 2017 talks on behalf of TG9 were presented by Axel Benner at the CEN-IBS (Central European Network of the International Biometrics Society) conference (Vienna, Austria, August 2017) and by Jörg Rahnenführer, Harald Binder and Axel Benner at the GMDS (German Association for Medical Informatics, Biometry and Epidemiology) conference (Oldenburg, Germany, September 2017).

Call for Contributions!

Thanks to everyone who contributed to the creation of the inaugural STRATOS Newsletter! We look forward to hearing about this year’s achievements and showcasing them in the next issue. Keep up the great work—it is through all of your efforts that the STRATOS Initiative continues to grow and thrive! Please collect stories and ideas for the next newsletter.

All contributions are welcome!

Please send contributions to Willi Sauerbrei (wfs@imbi.uni-freiburg.de).

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