Expert workshop on subgroup analysis

Workshop report

Report of the workshop held on 18 November 2011 at the European Medicines Agency
Disclaimer

This report was sponsored by the European Medicines Agency in the context of the Workshop on Subgroup Analysis. Although the conclusions it contains have been endorsed by the Agency, the views expressed are those of the authors and do not necessarily represent an official position of the Agency.
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1. Agenda

Analysis of subgroups is important in every confirmatory trial to assess internal consistency.

Sometimes subgroup analysis are used with the intention to rescue trials that ‘fail’ based on the overall population or to try to identify patient groups with the most favourable benefit-risk profile.

Subgroups should be pre-specified in the trial protocol, based on demographic, genomic or disease characteristics (e.g. sub-entities of a disease that are widely recognised within the medical community) but may also materialise based on a need or desire to further explore study results.

Formal statistical methods for investigating the homogeneity of the treatment effect across subgroups do exist and these are used by companies or regulatory bodies to provide re-assurance or to challenge the applicability of overall findings to subgroups.

In addition, simpler (often visual) methods can be helpful in elucidating and displaying results from subgroups. In some dossiers, the investigation of results in subgroups is minimal, perhaps in fear of (possibly false) negative findings that may complicate assessment.

Objectives of the workshop

- To present the scope and content of the proposed guidance document to internal and external experts to receive feedback for further reflection. To discuss the role of subgroups in the assessment of clinical trials, including:
  - Is it important to consider subgroup findings in the assessment of all confirmatory clinical trials? Have all important uses of subgroup analyses (in terms of regulatory assessment) been highlighted in the Concept Paper?
  - When should subgroup findings be incorporated in the assessment? What statistical methodology is available to incorporate findings in the most reliable way?
  - What are the consequences of incorporating subgroup findings in the assessment on the decision making procedure?
- To discuss standards and methods for planning, conducting and reporting ‘confirmatory’ subgroup analysis as distinct from (exploratory) subgroup analyses to assess internal consistency of study results and as distinct from post-hoc subgroup analyses aiming to rescue a ‘failed’ trial or improve the expected trade-off of benefits and risks compared to the whole trial population.
- To discuss standards and methods for planning, conducting and reporting ‘exploratory’ subgroup analysis, including statistical approaches that assist in drawing inferences when multiple subgroup analyses are performed.

Organising Committee

Rob Hemmings, Medicines and Healthcare Products Regulatory Agency, UK
Armin Koch, Institute for Biometry, Hannover Medical School, Germany
Norbert Benda, Federal Institute for Drugs and Medical Devices, Germany
Martin Posch, European Medicines Agency, UK
Marisa Papaluca, European Medicines Agency, UK
Programme chairpersons:

**Session 1:** Bruno Flamion, University of Namur, Belgium

**Session 2:** Norbert Benda, Federal Institute for Drugs and Medical Devices, Germany

**Session 3:** Armin Koch, Institute for Biometry Hannover Medical School, Germany

**Session 4:** Bruno Flamion, University of Namur, Belgium

List of speakers

- Robert Hemmings
- Armin Koch
- Sue-Jane Wang
- Oliver Keene
- Alex Dmitrienko
- Kevin Carroll
- Nigel Stallard
- Frank Bretz
- Kit Roes
- Christine Fletcher
- Martin King
- Stefan Lange
2. Abstracts

Session 1: Current guidelines and expectations on subgroup analysis in regulatory decision making

Chairperson: Bruno Flamion, University of Namur, Belgium

"Subgroup analyses in regulatory decision making"

By Rob Hemmings, Medicines and Healthcare Products Regulatory Agency, UK

Subgroup analyses present a particular set of methodological problems for those designing, analysing and interpreting clinical trial data, including the pharmaceutical industry as clinical trial sponsors and the regulatory system. This presentation will describe these problems from a CHMP perspective and will present the motivation and the philosophy behind the regulatory guidance document that is being discussed.

Feedback on the presentation to influence the forthcoming guidance document was sought.

“Reliably basing conclusions on subgroups in significant and non-significant clinical trials” – Click

By Armin Koch, Institute for Biometry, Hannover Medical School, Germany

In some instances a license has been restricted to a subgroup of a formally significant clinical trial and in other instances a license has been granted for a subgroup of a formally non- or borderline significant trial. Examples are presented to support the view that well defined subgroups are an important source of information about efficacy and safety of a new drug or a known drug in a new indication. The forthcoming guidance document on subgroups of clinical trials will concentrate on assessment strategies for clinical trials in this aspect and show how this assessment can be guided at the planning stage. The decision, whether a positive conclusion can be based on a non-pre-specified subgroup of a clinical trial will always be a case by case decision. Nevertheless some guiding principles may be of help to guide this decision making process.

“A subgroup or a subpopulation – design and analysis issues in clinical trials”

By Sue Jane Wang, Food and Drug Administration, USA

Traditionally subgroup analyses are routinely performed in controlled clinical trials to assess the consistency of subgroups relative to the overall treatment effect obtained from intent to treat patients. In regulatory submissions, enrichment strategy has been one type of study designs to assess treatment effect in a relatively narrowly defined patient subgroup based on clinical features thought to be more homogeneous and to increase the study power. With the advent of genomics, the concept of subgroup has gradually been elevated to subpopulation due to the belief of potentially more accurately defined molecular targets. This presentation used the term ‘subset’ as a general term that may refer to as a subgroup or a subpopulation. Although pre-specification of a subset hypothesis can make the subset analysis more credible than post-trial subset analyses, this presentation distinguished between subgroup versus subpopulation. Pre-trial versus a variety of on trial predictive enrichment was introduced. The utility of each strategy including design consideration, analysis approaches, case examples and regulatory perspectives were presented and discussed. Some may be more suitable for
learning purpose while others may be considered confirmatory.
Keywords: biomarker classifier, predictive enrichment, subset, subpopulation

“Subgroup analysis: a view from an industry statistician”

By Oliver Keene, GlaxoSmithKline, UK

Subgroup analysis is of major interest to regulators, payers, the Pharmaceutical industry and patients. All parties are concerned to find which if any groups derive a positive risk-benefit from a new medicine. However, subgroup analysis represents a major statistical challenge and it is very hard to identify in a single clinical trial what is a true difference in effects as opposed to a false positive finding. This is because of the number of potential subgroups available for analysis and the large potential for effects to differ among levels of a covariate by chance. Confusion often arises when discussing subgroup analysis where the placebo outcome varies across different levels of a covariate. For some endpoints, a treatment may have the same effect on the relative scale but if the baseline risk differs, this can translate into different benefits on the absolute scale. Where a covariate is measured on a continuous scale e.g. age, it is common practice to classify patients into subgroups based on different cut points. Such practice loses information and it is preferable to model the response via a continuous covariate.

The need for subgroup analysis is related to the overall patient population enrolled as defined by the inclusion/exclusion criteria and how diverse that is. The more homogeneous the population studied, the fewer requirements there should be for subgroup analyses, but this may have implications for generalisability.

In order to limit the extent of post-hoc subgroup analysis, there is a need for increased focus and discussion on subgroups at design stage. Pre-agreement with regulatory authorities on important subgroups may be helpful. Historically, the focus of subgroup analysis was on identifying subgroups where the treatment effect is larger than that observed in the overall trial. However, the need now in regulatory terms is to show consistency of effect across different categories of a covariate. Sponsors often assume consistent effects of treatment across the trial population and seek to explain any different effects in subgroups as due to chance. On the other hand, regulators may expect effects to vary across subgroups and can ask the sponsor to establish that the risk-benefit is acceptable for each subgroup.

However, in practice consistency of effect is difficult to define. Interaction tests are of limited value and any requirement for each subgroup to show a given level of effect is problematic. Bayesian approaches may be potentially useful but these tend to start with the prior belief that the effect in a subgroup will reflect the overall trial result. The new guideline on subgroup analysis needs to balance any increased requirements to show consistency of effect with appropriate consideration of the level of evidence that sponsors are required to provide before a patient in a particular subgroup may receive a new medicine.

Disclaimer: The views expressed above are personal and do not necessarily represent those of GlaxoSmithKline or of the Pharmaceutical Industry in general.
Session 2: 'Confirmatory' conclusions based on subgroups

Chairperson: Norbert Benda, Federal Institute for Drugs and Medical Devices, Germany

"Multiple testing methodology in the context of subgroup analysis"

By Alex Dmitrienko, Quintiles Innovation, USA

This talk focussed on clinical trials with a fixed design that include evaluation of treatment effects in target subpopulations (defined by demographics, clinical and genetic markers) in addition to standard analyses in the overall population. Inferences in the subpopulations are independent of inferences in the overall population and thus may result in regulatory claims even if there is no evidence of a beneficial effect in the overall population. This talk provided a summary of methods for addressing multiplicity issues arising in clinical trials with target subpopulations, including the general formulation of the multiplicity problem and key principles used in the development of multiplicity adjustments. Specifically, it is important to account for logical relationships among the tests in the individual populations (i.e., account for the fact that the individual populations are interchangeable) and available distributional information (i.e., account for positive correlations among the test statistics in this multiplicity problem). The principles were illustrated using more basic non-parametric multiple testing procedures and more powerful parametric multiple testing procedures and recommendations were provided. In addition, statistical considerations related to the assessment of influence and interaction were presented. The influence condition states that the beneficial effect of treatment must not be limited to only the target subpopulations and the interaction condition states that the treatment effect in a target subpopulation should be appreciably greater than the treatment effect in the overall population. A decision-making process based on the assessment of the influence and interaction conditions was introduced to help formulate regulatory guidelines to support broad and restricted labeling.

“Efficacy claims and subset analyses in phase III: some thoughts and examples”

By Kevin Carroll, AstraZeneca, UK

Subgroup analyses are common place in PIII trials. Forest plot displays of multiple subset analyses are now routinely seen in publications of trials results, primarily as a visual aid to allow an informal judgment of the 'consistency' of the overall result. Despite this, there is currently no agreed regulatory framework for the conduct and interpretation of such analyses, nor of their potential implications on product labeling and regulatory licensure. The presentation focussed on the broader questions relating to the use and utility of subgroup analyses in confirmatory Phase III trials where such analyses are intended:

- To provide an assessment of internal 'consistency' in a trial with an overall positive outcome.
- By design to formally assess the hypothesis of efficacy in a predefined subset.
- To salvage a negative trial.

The issues were illustrated with real examples.
“Adaptive clinical trials with subgroup selection”
By Nigel Stallard, University of Warwick, UK

If a clinical trial is planned to compare two treatments in both a pre-defined subgroup and the full population, with these considered as co-primary analyses, it is important that the statistical approach leads to control of the family-wise type I error rate. In such a setting, if recruitment is slow relative to the length of time taken to observe the outcome, it may be efficient to conduct an interim analysis to decide whether to focus on the comparison in the full population, subgroup or both in an adaptive design. In this talk a new method was proposed for such an adaptive design based on the conditional error function principle and a test utilising knowledge of the correlation between test statistics obtained from the full sample and subgroup. The methodology is generic in that it is based on normal test statistics rather than specific assumptions about the distribution of the data. Results of a simulation study based on a real trial with subgroup analysis were reported. These indicated that the new method is more powerful than previously suggested adaptive design approaches for trials of this type, which are, in turn, more powerful than conventional fixed sample size designs.

“Confirmatory subgroup analyses: Case Studies”
By Frank Bretz, Novartis Pharma AG, Switzerland

Exploratory subgroup analyses are often used to assess internal consistency of study results or to rescue a failed trial by assessing the expected risk-benefit compared to the whole trial population in a post-hoc manner. In this presentation the focus was on planning, conducting and reporting confirmatory subgroup analyses, where one or more subgroups are pre-specified in the trial protocol, based on demographic, genomic or disease characteristics. Several case studies were reviewed to illustrate the variety of applications and then present a in detail a confirmatory adaptive designs with Bayesian decision tools for a targeted therapy in oncology.

Session 3: The role of subgroup analysis in the assessment of clinical trials
Chairperson: Armin Koch, Institute for Biometry Hannover Medical School, Germany

“Perspectives on analysing subgroup effects of clinical trials and their meta-analyses”
By Kit Roes, Clinical Research University Medical Centre Utrecht, Netherlands

The analyses of subgroups or subpopulations in clinical trials are common in the medical literature and an important guidance for treatment decisions by physicians and treatment guidelines. Nevertheless, assessing the level of evidence of differential treatment effects (efficacy or safety) between subgroups is a methodological challenge. In addition to multiplicity and replication issues, problems known from epidemiological studies affect data analysis and interpretation. Based on examples from meta-analyses and individual studies it was demonstrated that treatment guidance for subgroups can be assessed and prediction models to guide treatment decisions can be based on clinical trial results. For such approaches modelling is more appropriate than assessing differences in multiple dichotomous splits of the data. These modelling approaches do stretch the regulatory decision making and may initially be appropriate as additional relevant information at the time of licensing.
“Subgroup analyses: from nasty business to stratified medicine – an HTA perspective”
By Stefan Lange, Institute for Quality and Efficiency in Health Care, Germany

When interpreting the results of clinical trials, the validity of subgroup analyses is traditionally seen to be questionable. Subgroup analyses may have a multiplicity problem; and such analyses carry an additional high risk of bias, if they are data driven. However, within the framework of systematic reviews and health technology assessments (HTA), subgroup (or related) analyses have a certain relevance, as they serve as an instrument to explain observed heterogeneity. Moreover, legal requirements exist (e.g. in Germany) that necessitate the specific identification and analysis of subgroups. Last but not least, adequately conducted subgroup analyses are an essential prerequisite for so-called personalized (or better “stratified”) medicine. The latter leads to question as to whether in future it might be appropriate not to assume from the outset that treatment effects within individual studies are homogenous, but also to interpret results of individual studies more in the sense of a meta-analysis and to test for heterogeneity.

“Use of subgroups to ‘rescue’ a failed trial or improve benefit-risk”
By Martin King, Abbott Laboratories, USA

When a trial does not demonstrate a statistically significant treatment effect for the overall population, analysis of a subgroup only identified post hoc is generally understood to be inadequate for regulatory approval. Conversely, when a subgroup is pre-specified and the analysis plan includes evaluation of both the overall population and the subgroup (with appropriate control of the type I error rate), it may be straightforward to approve the treatment in the pre-planned subgroup.

Many situations, however, fall somewhere in between these two easily managed scenarios, and the appropriate course of action may be more difficult to determine. In this presentation we used the recently published ACCORD Lipid trial as a case study to illustrate one such example.

The treatment studied in ACCORD Lipid was approved, prior to the trial, for a particular group of patients, based on its effect on biomarkers. ACCORD Lipid, a cardiovascular outcomes trial, was conducted in a much broader population than that described by the product labeling; the product’s original approval was thus in a “subgroup” of the population enrolled in the trial. The trial did not show a significant treatment benefit in its overall population, but in patients with characteristics consistent with product labeling, there was a nominally statistically significant result.

For potential safety findings in subgroups, somewhat different considerations apply when determining the appropriate course of action, which could range from the conclusion of a chance finding to restriction of the treatment’s indication to the complement of the subgroup. The ACCORD Lipid trial provides a useful example of this situation, with a nominally significant treatment-by-gender interaction that included a treatment effect estimate in the wrong direction (i.e., a potential safety signal) in women.

Considerations for evaluating efficacy and safety subgroup findings were discussed, interactions between the sponsor and regulatory authorities regarding the ACCORD Lipid trial described, and corresponding regulatory actions summarized.

“Panitumumab: The KRAS Story”
By Chrissie Fletcher, Amgen, UK

The panitumumab case study summarised the steps that were undertaken to plan, conduct and report the subgroup analyses for KRAS, a predictive clinical biomarker for treating patients suffering from metastatic colorectal cancer. The impact of KRAS to the drug development program was described
including a summary of the key changes made to accommodate the predictive biomarker in the other ongoing panitumumab clinical trials.

**Session 4: Plenary discussion and closing remarks**

Chairperson: Bruno Flamion, University of Namur, Belgium

The point was to share views and recent information about the use of subgroup analyses during the planning and assessment phases of exploratory but also especially confirmatory clinical studies during novel drug developments. Subgroup analyses present a particular set of methodological problems for those designing, analysing and interpreting clinical trial data, including the pharmaceutical industry as well as clinical trial sponsors and the regulatory system. The CHMP is in the process of drafting a guideline on The Use of Subgroup Analyses in Randomised Controlled Trials and welcomes all fruitful comments.

Examples were presented by industry, academic and regulatory experts during the meeting and lively discussion ensued. The main conclusions of the meeting were:

a) With regards to the design of trials:

- Despite all efforts to achieve homogeneity, clinical trial populations are frequently heterogeneous and regulators have a responsibility to examine the benefit/risk balance not only in the average patient but also in subsets of patients defined by biological or clinical characteristics besides traditional demographics such as gender, age, and ethnicity. Therefore, plans to explore benefits and risks in biologically defined and potentially clinically relevant subgroups should be incorporated into every development program.

- Early dialogue between industry and regulators (and possibly health technology assessment bodies which may have different preferences in the interpretation of subgroup analyses) about the most important subgroups to be accounted for in the design of the trial was considered highly valuable and will guide assessment.

b) With regards to the analysis of trial results:

- Statistical methods to investigate the consistency of effects across the entire target population were discussed (tools are not limited to interaction tests), as well as methods to deal with multiplicity issues to control the probability of false positive or false negative findings. Heterogeneous results across subsets will require a further level of scrutiny in the assessment phase. A quantitative definition of internal consistency does not exist.

- Post-hoc subgroup analyses to improve decision making should be interpreted with particular caution but should not be ruled out a priori; these analyses may convey very important information about the right target population. However, they pose difficult challenges for the assessment as the level of evidence of results from post hoc analyses can hardly be statistically quantified. Whilst relevant to all subgroup investigations biological plausibility and replication across studies, e.g. in the same therapeutic class, seem to be factors of particular importance to accept or reject post-hoc analyses. It was also agreed that this point needs refinement and could be discussed in detail in the upcoming guideline.
The participants of the workshop agreed that ultimately it is essential for the benefit of patients that subgroup analyses are based on rigorous methodology balanced with pharmacological and clinical plausibility such that conclusions are guided by the overall strength of evidence.

3. Biographies of the chairpersons and speakers

**Bruno Flamion**

Bruno Flamion is a Belgian national; a graduate from the medical school of the University of Brussels, summa cum laude (MD, 1983); a specialist in internal medicine and nephrology (1988); and earned a PhD in Physiological Sciences (1992). He was a research fellow at the National Institutes of Health in Bethesda, MD, United States (1988–1992) and for the Belgian National Fund for Scientific Research (1992–1996).

Currently, Bruno is a full professor of physiology and pharmacology at the University of Namur, Belgium (since 1998) and head of the laboratory of physiology and pharmacology (since 1996). Additionally, he has continued his activities in basic research (hyaluronan, hyaluronidases).

Bruno is a medical and pharmacological expert for the Belgian Federal Agency for Medicinal and Health Products (since 1999) and a member of the regulations advisory board of the Centre for Innovation in Regulatory Science (CIRS), formerly CMR (since 2005).


Bruno is also chair of the Belgian federal Committee for Reimbursement of Medicines (CTG/CRM), a part of the National Institute for Health & Disability Insurance (RIZIV/INAMI) (since April 2010).

**Robert Hemmings**

Rob is a professionally qualified medical statistician. He has been with the Medicines and Healthcare products Regulatory Agency (previously Medicines Control Agency) for 11 years and heads the group of medical statisticians. Much of Rob’s time is spent educating medical colleagues in the importance and...
artistry of clinical trial statistics; their use in proof and in obfuscation. Rob currently holds the following positions within the European drug regulatory system:

- **CHMP member:** CHMP is the body responsible for preparing the opinions of the European Medicines Agency on all questions concerning medicinal products for human use. Rob is one of the 32 voting members of this key European committee.

- **Chair of the CHMP’s Scientific Advice Working Party (SAWP) with responsibility for preparing advice to the pharmaceutical industry on the appropriate tests and trials to conduct in the development of a medicine for marketing authorisation.** This group includes approximately 50 regulatory scientists from across the European regulatory network and handles approximately 400 scientific advice / protocol assistance and qualification of biomarker procedures each year.

- **Rob is also a member of CHMP’s Biostatistics working party with responsibility for giving advice on matters relating to clinical trial methodology across the EU regulatory network.**

Rob regularly speaks at national and international scientific meetings on a broad range of topics relating to medical statistics and drug licensing.

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**Armin Koch**

Armin Koch received his Diploma in Mathematics from Heidelberg University in 1988. He has been working as a Research Assistant at the Department of Biostatistics at the German Cancer Research Centre and wrote his thesis in Medical Biometry at the department of Biometry of the Medical Faculty at the University of Heidelberg.

From 1999 to 2008 he has been working at the Federal Institute for Drugs and Medical Devices (BfArM) in Germany and was head of the Biostatistics Group from 2002 onwards and head of the Biostatistics and Pharmacokinetics Group since 2005.

Since September 2008 he is the Director of the Institute for Biometry at Hannover Medical School. Pr. Koch is a member of the Scientific Advice Working Party (SAWP) and the Biostatistics Working Party (BSWP) of the Committee for Medicinal Products for Human Use (CHMP) at the European Medicines Agency (EMA) in London.

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**Sue Jane Wang**
Dr. Sue-Jane Wang is Associate Director for Adaptive Design and Pharmacogenomics and the Biostatistics Leader for the Biomarker Qualification Program from Office of Biostatistics, Office of Translational Sciences in Centre for Drug Evaluation and Research, U.S, Food and Drug Administration. The subgroup topic due to this workshop is a critical component in pharmacogenomics that ties in with biomarkers for phase 3 drug development. Dr. Wang was the first statistical scientist representing Centre for Drug Evaluation and Research of FDA to receive an individual FDA-level Scientific Achievement award. She has served as an Editor-in-Chief for Pharmaceutical Statistics. Currently, she is an elected member of International Statistics Institute, an associate editor for Statistics in Medicine and for Statistical Biosciences Journal. She has published more than 80 peer reviewed papers in statistical, medical, genomics, and bioinformatics journals. She is a fellow of American Statistical Association.

**Oliver Keene**

Oliver is a Biostatistics Director in the respiratory area at GlaxoSmithKline. Oliver started at Glaxo in the pre clinical area over 25 years ago. He spent several years leading statistical support to Clinical Pharmacology in the UK. He subsequently moved to later stage clinical projects and has worked on therapeutic areas as diverse as anti-virals, arthritis and cardiovascular. Oliver was chair of the PSI (Statisticians in the Pharmaceutical Industry) regulatory committee for five years. Oliver has published widely on applications of statistics to clinical trials including papers on ITT analysis and analysis of recurrent event data.

**Norbert Benda**

Norbert Benda is the head of Biostatistics and Special Pharmacokinetics Unit at the Federal Institute for Drugs and Medical Devices (BfArM) in Bonn, Germany, since February 2010. He is member of the EMA Biostatistics Working Party and alternate member of the EMA Scientific Advice Working Party. Before he joined the BfArM he gained a 12-year experience as a statistician in the pharmaceutical industry. He worked in the Statistical Methodology Group at Novartis Pharma AG Basel and as a Statistician for Schering AG Berlin. Prior to that, he was employed as a lecturer in biostatistics at the University of
Tübingen. He obtained a PhD in mathematical statistics from the Free University of Berlin and graduated in mathematics from Aachen University (RWTH Aachen, Germany).

**Alex Dmitrienko**

Alex Dmitrienko, PhD, Executive Director, Quintiles Innovation, has been actively involved in biostatistical research and has published over 60 papers on multiple testing procedures and analysis of safety data in clinical trials. He has authored/edited two SAS Press books (Analysis of Clinical Trials Using SAS, Pharmaceutical Statistics Using SAS) and a Chapman and Hall/CRC Press book (Multiple Testing Problems in Pharmaceutical Statistics). He is an Associate Editor for Statistics in Medicine and Biometrics and a Fellow of the American Statistical Association.

**Kevin Carroll**

Kevin is currently VP Statistics & Chief Statistical Expert at AZ R&D where he is accountable for the technical content and veracity of statistical argument supporting drug development programmes and product license applications across all of AZ’s therapeutic areas. Kevin has published on a wide variety of statistical issues in drug development including issues around non-inferiority, the design of outcome trials, and the use of PFS in oncology, surrogacy and the utility of biomarkers in trial design. He has also had practical experience of regulatory issues relating to subgroup analyses some of which he will be touching on today.
Nigel Stallard

Nigel Stallard is Professor of Medical Statistics, head of the Statistics and Epidemiology group and Deputy Head of the Division of Health Sciences at Warwick Medical School, University of Warwick, UK. Following a degree in Mathematics at Cambridge University, Professor Stallard started his career as a mathematical modeller at the Royal Air Force Institute of Aviation Medicine in Farnborough, before moving into statistics. He studied part-time for an MSc in the Department of Applied Statistics at the University of Reading prior to joining the department as a Research Fellow in 1992, also obtaining a PhD from the department in 1995. He was a founding member of the Medical and Pharmaceutical Statistics Research Unit at the University of Reading and remained there for thirteen years until moving to Warwick in 2005. Throughout his career, in addition to building a portfolio of methodological statistical research work, he has collaborated widely with researchers and clinicians in industry, academia and the public sector. Professor Stallard’s primary research interests are in the statistical design and analysis of clinical trials. Within this broad area, his particular expertise is in the optimal design of early phase clinical trials and in methodology for the design and analysis of adaptive or sequential confirmatory clinical trials with interim analyses and adaptations such as treatment selection. His most recent work focuses on the use of short-term endpoint data for decision-making during the course of a clinical trial. Current work of his on this problem, being undertaken collaboratively with colleagues from Warwick, Reading and Goettingen, is funded by the UK Medical Research Council.

Frank Bretz

Dr. Frank Bretz joined Novartis in 2004, where he is currently Global Head of the Statistical Methodology group. He has supported the methodological development in various areas of drug development, including dose-finding, multiple comparisons, and adaptive designs. Since 2007 he is an Adjunct Professor at the Hannover Medical School.
Kit Roes

Kit Roes is Professor of Biostatistics at the Julius Center of the University Medical Center Utrecht and head Quality Assurance of Clinical Research. His experience includes over 15 years in research and development in the pharmaceutical industry and life sciences research and 10 years of experience in industrial statistics. He is past president of the European Federation of Statisticians in the Pharmaceutical Industry. He is advisor of the Dutch Medicines Evaluation Board and non-executive Director of Biostatistics and Clinical Development Strategy of Julius Clinical Research. He is Editor of Pharmaceutical Statistics. His research interests include design and analysis of clinical trials, causal inference and high dimensional data.

Stefan Lange

Stefan Lange, MD, PhD, completed his medical studies at the Heinrich-Heine-University in Düsseldorf in 1989 and received his MD in 1994. From 1989-1993 he was initially in practical training at the Ferdinand-Sauerbruch-Clinic in Wuppertal, then assumed the position of intern/resident physician. In 1993 he joined the department of medical computer sciences, biometrics and epidemiology at the Ruhr-University in Bochum and was appointed to the position of research assistant in 1995. He was awarded the certificate of Biometrics in Medicine with the title of "Qualified Statistician" by the German Association for Medical Computer Sciences, Biometry and Epidemiology (GMDS) in 1999. In 2003 he received his PhD (second thesis, the Habilitationsschrift) at the Ruhr University and received the venia legendi (right to teach) in Medical Biometry and Clinical Epidemiology. He joined the Institute for Quality and Efficiency in Health Care in 2004, and has held the position of Deputy Director of the institute since 2005. He headed the department of Non-Medical Interventions until 2007.
Martin King, PhD, is Director, Statistics at Abbott Laboratories. He has over 14 years’ industry experience in clinical trials design and research and development of new drugs. He has led statistical aspects of clinical research in several therapeutic areas, including HIV/AIDS, Cardiovascular/Dyslipidemia, Hepatitis C, and Oncology and he has authored or co-authored over 30 peer-reviewed publications and over 100 conference presentations.

Chrissie Fletcher, Director Biostatistics and Head of International Biostatistical Science, Amgen Ltd. Chrissie has worked in the Pharmaceutical Industry for 20 years, and is currently the Head of International Biostatistical Science at Amgen Ltd. Chrissie and her team support all phases of drug development, including the design, analysis and reporting of phase I-IV clinical trials and observational research studies for Amgen's product portfolio. Statistical support is also provided for regulatory and reimbursement filings, value evidence generation, and for post-marketing activities. Chrissie and her team are engaged in scientific research and methodological projects and keep abreast of trends in statistics and the Pharmaceutical Industry. Prior to joining Amgen, Chrissie was a project statistician at SmithKline Beecham Pharmaceuticals.

Chrissie is the Communications Officer for European Federation for Statisticians in the Pharmaceutical Industry (EFSPI), and member of EFSPI’s Operations Board. She also chairs the Statisticians in the Pharmaceutical Industry [PSI] Special Interest Group on Health Technology Assessments, is a member of the PSI Regulatory Committee, and is a Director of PSI.