European Statistical Meeting on Subgroup Analyses

On November 30th 2012, the EFSPI organized a one day meeting on Subgroup Analyses. Over 90 attendees with various backgrounds attended this meeting.

Prof Kit Roes from the University Medical Center of Utrecht opened the day. He discussed the results of a recent trial (DECS trial published in JAMA in Nov 2012) for which the overall effect of the primary endpoint was borderline missed. The trial is a perfect candidate to run subgroup analyses on (age subgroup in this example). He focused on the inflated Type I error and on the importance to preplan for subgroup analyses that make clinical sense. He also pointed to some enrichment designs that can anticipate on subgroups of interest.

Dr. Rob Hemmings (MHRA) provided the 2nd presentation of the day. Doing exploratory subgroup analysis can clearly lead to incorrect decisions, but on the other hand not performing any subgroup analyses may prevent you as well from better patient care; The problem is that the truth cannot be know from a single trial. A clinical rational of doing subgroup analyses is crucial, as well replication of results. He also emphasized that patients recruited to a clinical trial are not homogenous, therefore response to treatment should not be assumed to be homogenous. He discusses exploratory versus confirmatory subgroup analyses which he compared to science versus art.

Dr. Oliver Keene from GlaxoSmithKline provided his personal opinion regarding performing subgroup analyses. He agreed that it is very hard to identify if there is a true effect or if it is rather a false positive effect that is observed within a subgroup. He noticed that often categorical parameters are used for subgroup analysis (like age classes) and advised rather to use continuous subgroup parameters to avoid loss of information. He also advised to have a pre-agreement regarding subgroup analysis with regulatory and where possible to plan for a homogenous patient population as this makes subgroup analysis less required. He concluded with agreeing that it is very hard to define consistency of the treatment effect across subgroups, an interactions test might be helpful but have low power and therefore are of limited value.

Prof. Nigel Stallard (University of Warwick) presented the topic “Adaptive Clinical Trial Design for subgroup selection”.He provided a theoretical approach of a situation with 2 hypotheses of interest: one on the overall population and one on a predefined subgroup population. The trial was divided in 2 stages (separated by an IA), at the IA a pre-specified decision rule decided for the final hypothesis(es) of interest. Finally, he simulated the power comparing the adaptive design with a fixed design, using different types of combination functions and demonstrated the increased power when applying an adaptive design.

Dr. Frank Bretz (Novartis) presented the topic “Multiplicity Considerations in Confirmatory Subgroup Analyses”. He started by illustrating the major scientific concern about multiplicity; the lack of reproducibility. He then discussed the requirement for multiple test procedures for confirmatory subgroup analyses. He illustrated 3 theoretical case studies with different applications involving confirmatory subgroup analyses in which different testing procedures were applied for which the results determined the amount of Type I error to be spent to each hypothesis of interest. He concluded with a hypothetical example suggesting that strong FWER control may not always be appropriate

Dr. Nigel Baker (Amgen) presented the topic “Biomarker Defined Subgroups in Gastric Cancer, a Case Study”. First, he provided general background on the Gastric Cancer and biomarkers that can potentially be used to identify patients likely to benefit from drug. Then, he presented a Phase 2 study in which overall survival was not significant in overall population, but where greater improvement was seen in the subgroup of patients with high levels of a tumor biomarker. He concluded that these results accommodated for planning a phase 3 trial to confirm the efficacy of drug in patients with the biomarker-positive.

Dr. Gerd Rosenkranz (Novartis) presented the topic “Case Studies of Confirmatory Subgroup Analyses”. He presented different studies with confirmatory subgroup objectives and discussed some of the advantages and questions that were raised from these studies. He also pointed to power consideration to be taken into account (e.g., preference to power for the subgroup instead of overall population). In these case studies, he highlighted different approaches when designing clinical trials dealing with confirmatory subgroups, this included top-down from full population to subgroup(s), bottom-up from subgroup(s) to full population, or equal importance of total population and/or subgroup(s).

Dr. Jean-Marie Ledeine (Bristol-Myers Squibb) presented the topic “Genomic Status in Optimizing Subgroup Patient Selection: a case study”. He first presented a Phase 3 case study where positive results supported original marketing approval, but then pointed out to a genomic marker that predicted response to the study drug which was discovered (after submission), resulting in changes in daily practices. FDA was approached about using the original study for a retrospective subset analysis to demonstrate the association between genomic status and treatment. He then showed results where benefit was only observed in the non-predictive marker subgroup, results that were supported by various sensitivity analyses that addressed the concern of missing genomic marker status using different techniques of imputing missing data (MI, worst/best case scenario).

A lively panel discussion closed the meeting.
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