European Federation of Statisticians in the Pharmaceutical Industry
Representing Statistical Associations in Europe

EFSPI Newsletter November 2014

In this newsletter:

Regulatory Update

EMA Workshop on Subgroup Analyses

On the 7th November, EMA hosted a 1-day workshop on subgroup analyses. Regulators from Europe, opened the meeting by reminding the audience for the rationale for developing the draft EMA guideline on subgroup analyses, and regulatory views on subgroup analyses were presented by representatives from FDA and Japan. A summary of the main issues identified from the ~20 stakeholders (including EFSPI) where ~150 pages of comments received was provided, and there was a great deal of consensus across the various stakeholders. These main issues included requests for the goal of the guideline to be made clearer, for the different types of subgroups to be better defined, to provide a definition of 'consistency', clearer recommendations about powering clinical trials for specific subgroups, further discussion on what impact subgroup analyses could have on product labels and regulatory decision making, increased emphasis on the role of subgroups in integrated (pooled) analyses across multiple clinical trials, and to align on terminology throughout the guideline. On behalf of EFSPI, Alan Phillips (ICON) presented the key statistical aspects highlighted in the EFSPI comments submitted to EMA on the draft guidance. A couple of Industry colleagues were invited to present proposals for emerging methodologies relating to how to assess consistency and methods for selecting and estimating treatment effects in exploratory subgroups. A Q&A session enabled the audience and the regulators to pose additional questions which allowed further discussion on many of the topics noted above. Click here to see details of the workshop.

In summary, whilst no significant 'new' information on subgroups emerged from the workshop, the audience was able to obtain an understanding of the views by the various regulatory agencies, and an appreciation there are many common areas of concerns by stakeholders. The EFSPI/PSI Regulatory Committee has identified the need to work on the statistical methodology and

interpretation of subgroup analysis. Of particular interest is how these approaches will relate to the criteria applied to conclude consistency across subgroups. If you have experience and expertise in subgroup analyses and are able to provide active input over the next 6-9 months, please could you contact Aaron Dane at aaron.dane@astrazeneca.com before the 19th December 2014.

E9(R1): Addendum to Statistical Principles for Clinical Trials on Choosing Appropriate Estimands and Defining Sensitivity Analyses in Clinical Trials

Defining the primary objective of a clinical trial in the presence of non-compliance to the protocol or non-adherence to the assigned treatment is crucial for the planned statistical analyses and the interpretation of the results. This raises the need for a structured framework to specify the primary estimand(s) (i.e. "what is to be estimated and how") aligned to the primary objective of the study. The missing data report released in 2010 by the National Academy of Science, “Prevention and Treatment of Missing Data in Clinical Trials”, recommends explicit specification of a casual estimand in the protocol of a confirmatory trial. In order to reflect the importance of this topic, ICH have decided to supplement its E9 guidance in the coming years with an addendum which will provide a framework to align trial objectives and statistical approaches, a clear definition of estimands, and how the choice of an estimand is linked to important considerations around trial design, conduct and analysis. Click here to see the ICH concept paper.

At the recent ICH workshop in mid-November 2014 held in Lisbon, Portugal, a kick-off meeting was held with the E9(Revision 1) working group tasked to create the addendum. Members of the E9(R1) working group include representatives from the regulatory bodies and Industry associations across the ICH regions with Rob Hemmings (MHRA) the rapporteur (lead) and Estelle Russek-Cohen (FDA) the regulatory chair. In Europe, Chrissie Fletcher (Amgen) and Frank Bretz (Novartis) are participating in the E9(R1) working group on behalf of EFPIA. At this first meeting, the E9(R1) working group discussed the definition of an estimand and using some preliminary examples, explored how estimands for different clinical trial settings could be defined. There was a general consensus in the working group on what constitutes an estimand and a general consensus on an improved framework for clinical trial planning, conduct, analysis and reporting. The working group felt an estimand should include the population of interest, the clinical outcome of interest, and the measure of effect intervention, for example ‘compare experimental drug X and placebo in terms of improving endpoint Y at time Z for all randomised patients, without regarding adherence to randomised treatment’. An improved framework would ensure the trial has a clear objective, an appropriate estimand is defined relevant to the trial objective, appropriate analysis methodology is chosen to derive an estimate of the estimand, and appropriate sensitivity analyses for handling data limitations, assumptions and analytic approaches. There was a consensus that trials could have more than one estimand and the structured framework would improve dialogue between sponsors and regulators. The working group is keen to prepare case studies to promote the understanding of estimands and sensitivity analyses to key stakeholders in the statistical and clinical communities. It is recognized there are important practical consequences such as on how trial protocols are written, ~~and~~ how trials are designed and what data is collected.

EFSPI/PSI has recently set up an expert group on estimands, led by Alan Phillips (ICON) who will be meeting in February 2015 where the output of this meeting will be shared with the E9(R1) working group. Further information from both the ICH E9(R1) working group and the EFSPI/PSI expert group will be shared across the European Statistics community and this topic will be included in agenda’s for further discussion at key statistical meetings and congresses during 2015. Please direct questions relating to the E9 addendum to Chrissie Fletcher (fletcher@amgen.com) and questions on the EFSPI/PSI estimand expert group to Alan Philips (Alan.Phillips@iconplc.com).

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Scientific Update

No scientific meetings are scheduled for the remainder of 2014. BBS with assistance of EFSPI had a successful seminar on "Data sharing in Clinical Development" on November 13. Meeting materials are available on the BBS (www.ceb-institute.org/bbs) and EFSPI (www.efspi.org) websites.

EFSPI is planning for three meetings in 2015; one meeting on **Dose Finding studies in Clinical Studies** in April; a second meeting on **Health Technology Assessments** together with the BBS in Basel in June 2015, and a third meeting after the summer break on **Biomarkers & Subgroups**.

In addition, we are planning for a webinar in the first quarter of 2015. If anyone has any suggestions of topics for discussion please email Egbert Biesheuvel (egbert.biesheuvel@ziggo.nl).

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Other Upcoming Events

PSI

PSI Training Course: Regulatory Interactions for Statisticians, 11th-12th February 2015, London. The course objective is to inform statisticians about the likely interactions they might have with regulatory agencies, both during a submission and at other times during drug development, and give advice on how to make these interactions most effective, Click here for further details.

PSI Training Course: Cross-over trial in Clinical Research, 4th – 5th March 2015, Heathrow, London. The emphasis is on practical matters: how should one plan and analyse cross-over trials if one is genuinely interested in finding out the effects of treatment. The approach is grounded in practical pharmacological considerations and unrealistic approaches to adjusting for carry-over will be avoided. The examples are all genuine. Click here for further details.

SCT/QSPI/FDA

The Society for Clinical Trials (SCT) and Quantitative Sciences in the Pharmaceutical Industry (QSPI) are holding a meeting with FDA to present Innovations in the Science and Practice of Clinical Trials December 9-10 2014 at the Universities at Shady Grove Conference Center in Rockville, Maryland, USA. Presentations will include sessions on small trials for rare diseases and large trials for rare events, on streamlining clinical trial operations, patient group engagement and regulatory efforts to include patient preferences in decision-making and on leveraging underutilized information sources in trial planning and analysis. More details and registration are available on http://meeting.sctweb.org/qspi.

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The World of Statistics

The World of Statistics movement has grown to a total of more than 2,350 organizations from countries across the globe. You can view the current participant and country lists by going to The World of Statistics website. To see the full list of The World of Statistics participating organization-sponsored events and activities around the world for the remainder of 2014, click here.

The second World Statistics Day will take place October 20, 2015. The event, which will be coordinated by the United Nations Statistics Division (UNSD), will operate under the theme, "Statistics for better decision-making—statistics for better development."

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And finally.....

If you are currently seeking to hire a statistician and wish to post a job advert, see the "Advertisements" area on the EFSPI website at www.efspi.org and view the "Job Postings" for instructions. EFSPI are offering one free advert for every 3 adverts posted on the website.

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