6th EFSPI Statistics Leaders Meeting

July 1, 2015, Brussels

Summary and Key Messages

Executive Summary

A high number of 26 people from 10 different countries representing 24 pharmaceutical companies or CROs attended the 2016 EFSPI Statistics Leaders Meeting, held in Brussels and hosted by MSD.

The agenda was a mix of follow up on important developments from previous years (Benefit Risk, Real World data, and Data Transparency) and completely new topics, such as the SIG Small Populations, and Estimands.

The Data Transparency Working Group (WG), set up by EFSPI, is finalizing a lot of their work in the five work streams and 4 papers are being prepared for submission. The general feeling is that the role and impact of biostatistics has been evident in this area to improve the reputation of the industry and increase data transparency. The WG was asked to stay on to monitor the first reports of analyses in the literature that are still to come and to think about agreements for data sharing between companies.

The increasing level of interaction of the EFSPI/PSI Regulatory Committee with the regulators in Europe was explained. For meetings later this year possible topics for discussion were brought up. The committee can still use new members, especially from mainland Europe.

A new SIG Small Populations was presented and opened for members. It will also have close contact with several other industry/governmental projects such as ASTERIX, IDEAL, and INSPIRE.

The impact in the business of Real World Data and the role of statisticians was extensively discussed. Compared to 2014 it seems that more companies are getting active in this area and the general feeling was that biostatisticians have to get themselves involved. There is clear need for best practices and RWE technical and leadership expertise that EFSPI could support.

The SIG Benefit Risk presented its achievements over the last period and focused in the discussion on ways to increase the contribution of statisticians in this area within companies as well as to increase the impact of the SIG and its work. As with the topic of real world data, next to access to best practices and expertise, also development of leadership and influencing skills will be key to statisticians to become a major player in this area.

Estimands was presented as a new topic and new framework for improved clinical trial planning, conduct, analysis and interpretation. The concept of estimands was explained and examples given as well as its context to the missing data problem and sensitivity analyses. More examples will help to better understand the underlying definition and issues but also to explain it in due time to the clinical colleagues. The Statistics Leaders are requested to give their input by providing feedback to set of questions raised at the meeting.

Organisation meeting

The Organizing Committee of the Statistics Leaders Meeting 2015 consisted of Stefan Driessen (Chair), Chrissie Fletcher, Hans-Ulrich Burger, and William Malbecq. The meeting took place in Brussels and was hosted by MSD. A high number of 26 people from 10 different countries representing 24 pharmaceutical companies and CROs was present. Another six registrants could not participate for various reasons, including train cancelations. Several new companies to the Forum were invited and their attendance and contributions broadened the representativeness of the meeting. For the first time also a small fee was charged for attendance in support of EFSPI's activities. This was discussed and agreed upon with the Forum of Statistics Leaders earlier in the year. The set up was to optimize time and quality of discussions and interactions (pre-reads, small round tables, short introductions to the topics, prepared set of questions).

Slides meeting

http://www.efspi.org/EFSPI/Statistics_Leaders_Meetings/Previous_Meetings/6th_Meeting_-_July_2015/EFSPI/Statistics_Leaders_Meetings/6th_Meeting.aspx?hkey=3a80fd69-05af-415f-8789-5d44d115fa7e

Welcome

Chair of the Organizing Committee of the Statistics Leaders Meeting 2015, Stefan Driessen, welcomed the 26 participants representing 24 pharmaceutical companies and CROs. The meeting took place in Brussels, hosted by MSD, and William Malbecq shortly introduced the company . The purpose of the meeting was explained followed by short recap of the action items from the 2014 Statistics Leaders Meeting to then swiftly move to the topics on the agenda.

Clinical Trial Data Transparency

Hans Ulrich Burger presented the current status of the EFSPI/PSI Working Group (WG) on Data Sharing that he leads together with Sally Hollis (see slides). All five work streams are close to finalization with several papers in submission process. General feeling is that reputation of Pharma has increased due to the increased transparency by data sharing and the role and impact of biostatistics has been evident and highlighted. Still the general impact is to be seen as no results have yet been reported back.

Feedback, action items, from the meeting:

- Accomplishments of the WG were well received and acknowledged
- Action WG: to work on the expected discussion on the "gentleman's agreement" that companies do not ask for each other's clinical study data. Will this hold for long?
    - Note: one of the companies mentioned that especially access requests are coming from academic centers from US, and almost none from Europe, which might turn out as a missed opportunity
- Action WG: to think about redefining that agreement from ethical or patient point of view and think about meaningful rules, if any, for data sharing between companies

Interaction with Regulators in EU

Christoph Gerlinger presented the activities of the EFSPI/PSI regulatory committee (see slides). The regulatory committee is facilitating commenting guidelines for which they can always use support. It has also started to meet with regulators in EU. They will meet again with MHRA statisticians in September again and with EMA's Biostatistics Working Party BSWP in October.

Feedback, action items, from the meeting:

- Action Statistics Leaders: to provide additional questions to the agency statisticians.
    - topics coming from meeting: use of Bayes statistics, differences between FDA and EMA (e.g., on non-inferiority margins)
- Action Statistics Leaders: to provide support to comment on EMA's upcoming reflection paper on statistical issues in CMC.
    - Bruno Boulanger from Belgium volunteered to take the lead. PMN: two colleagues from Germany and Switzerland expressed their interest in the meantime.
- Action Statistics Leaders: to encourage their staff to take seat in regulatory committee
    - Post meeting note: two colleagues have shown interest

SIG Small Populations

Egbert Biesheuvel presented the new SIG Small Populations (see slides). The purpose of the SIG was explained as well as its possible roles in relation to FP7 projects as ASTERIX (Advances in Small Trials dEsign for Regulatory Innovation and eXcellence), IDeAl (Integrated Design and AnaLysis of small population group trials), and InSPiRe (Innovative methodology for small population research).). In addition the special EFSPI/PSI commitments to the ASTERIX project were mentioned.

Feedback, action items, from the meeting:

- Action SIG: to present the SIG Small Populations in the EFSPI Newsletter
    - Stats Meeting favoured as name Small Populations over Rare Diseases
- Action Statistics Leaders: to inform their staff about the SIG and support membership
- Action SIG: to pay attention to confidentiality items in case of scientific insights coming from ASTERIX project

SIG Update

Stefan Driessen presented short update on the SIGs (see slides). A new SIG was mentioned: Application and Implementation of Methodologies in Statistics (AIMS).

Feedback, action items, from the meeting:

- Set up of such a SIG was well received
- Stats Leaders Meeting to inform SIG: there is interest to implement R in a validated fashion in production environment (could be small subgroup in AIMS).

Benefit Risk (SIG B/R)

Alexander Schacht, co-chair of EFSPI SIG Benefit Risk, shortly presented the composition and achievements of the SIG over the last years before concentrating on the role statisticians can or should play in this area and the best way the SIG can support this, using a set of well-prepared questions to the forum.

Feedback, action items, from the meeting:

- There is great need for (more) best case practices
    - Some companies mentioned pilots that worked out well
- ICH M4 is working on a B/R guideline; SIG may try to contribute
- SIG can highlight the blue–print that was developed of the role statisticians can play
- SIG can use new members; it can help recruitment to indicate that one does not need to be an expert to join the SIG, and also to indicate how much time it generally will take
- Influencing skills is an important attribute for statisticians to be successful in this multi-disciplinary area. It is recognised as a special topic:
    - Statistics Leaders could utilize the non-profit possibilities in the area of influencing skills
    - Reference was made to work by Lisa laVange on propagating leadership in statistics

Real World Evidence (RWE)


Armin Schüler and Hans-Ulrich Burger jointly introduced the emerging topic of Real World Data in our businesses to quickly come to a set of questions that spurred (separate) round table talks and plenary discussions. Compared to the 2014 meeting it seemed that more companies are getting active in this area and the role of statisticians was extensively discussed.

Feedback, action items, from the meeting:

- General feeling is that RWE is of growing importance and biostatisticians should get involved
    - it adds to RCTs (generalizability, filling gaps)
    - it gives opportunities to show added value
    - it is, however, not priority yet in most stats groups
- RWE requires different mindset and expertise
    - it is not RCT; issues as bias, confounding, data quality play important role
    - biostatisticians have right background to become SME but need help
- RWE is multi-disciplinary
    - joint effort between biostatistics, informatics, epidemiology and medics
    - in some companies dedicated groups are being set up for RWE
    - biostatisticians need not lead but need to contribute (debate, challenge, and drive for solutions)
- Action EFSPI:
    - to keep supporting exchange of information and experience in RWE
    - promote SIG RWE (formerly known as SIG Pharmaco-Epidemiology)
    - support sharing best practices and case studies
- Action Stats Leaders:
    - Support SIG RWE (resources, case studies)
    - Promote biostatisticians get involved in RWE

Summary conclusion RWE session:

- Biostatisticians have to take on their role in this area and get themselves involved
- Need for best practice examples and education on RWE technical and leadership expertise
- Organisation within pharmaceutical companies should be adapted to cover RWE
- EFSPI support of the development process fully appreciated and should continue

Estimands

Chrissie Fletcher, one of the EFPIA representatives on the ICH E9 Working Group, presented on "Estimands". She explained that the E9 WG acknowledges this as a new topic and new framework for improved clinical trial planning, conduct, analysis and interpretation, and that it is not only a missing data problem. The definition of estimand was given and the role of sensitivity analyses was explained in this context with an illustrative (diabetes) example. A set of questions was brought to the forum which led to a very lively and good discussion.

Feedback, action items, from the meeting:

- Potential bias seems to be underpinning the estimand discussion. It might be helpful to contextualise some of the rationale for why alignment on estimands and subsequent sensitivity analyses is given relative to considerations of potential biases
- Range of examples would be appreciated to better help understanding the differences between estimands (incl. use of graphics)
- Defining what the role of sensitivity analyses is would be helpful
- The involvement of clinicians is very important as it is understood this is not just a statistical issue
- Action Stats Leaders:
    - Send written response on the seven questions to Chrissie by beginning of September

Statistics Leaders Meeting 2016

Stefan Driessen mentioned that volunteers to help organize the 2016 meeting are very much welcomed. Also ideas for next year's meeting were explored: possible external speakers (Regulatory, IQWIQ), Biomarkers and Personalized Medicine, adaptive designs, risk based monitoring.

Closure of the Statistics Leaders Meeting 2015

Appendix 1: **AGENDA Statistical Leaders Meeting 2015**

Wednesday, July 1, 2015
Brussels, Belgium
MSD facilities

Time	Topic	Presenter / Facilitator
8:30-9:00	*Registration*	

9:00 - 9:15	• **Welcome address + Intro**
	  ○ Org. Ctee
	  ○ EFSPI President
	  ○ Recap Stats Leaders meeting 2014
		Stefan Driessen
		William Malbecq
		Chrissie Fletcher
		Stefan Driessen

9:15 – 9:45	• **Clinical Trial Data Transparency**
	  ○ Short Follow up 2014
	  ○ Role of Statistician
	  ○ Role in our Organizations
	  ○ Opportunities – Threats
		Hans Ulrich Burger

9:45 – 10:15	• **Interaction with Regulators in EU** ○ Short Introduction and Discussion	Christoph Gerlinger
10:15 - 10.45	*Coffee Break*	
10:45 – 11:15	• **SIGs – Update** • **SIG Rare Diseases** ○ Short Introduction + Discussion	Stefan Driessen Egbert Biesheuvel

11:15 – 12:30	• **Real World Evidence**
	  ○ Follow up 2014 (survey) & Present status
	  ○ Business case studies
	  ○ Statistician: role and skill set
	  ○ Opportunities – Threats
		Armin Schüler
		Hans Ulrich Burger

12:30-13:30	*Lunch break*	

Time	Topic	Presenter / Facilitator
13:30 – 14:30	• **SIG Benefit – Risk** ○ Follow-up 2012 - Achievements ○ New initiatives: technical and aspirational ○ Statistician: role and skill set ○ Challenges ○ Requests for advice, other issues	Alexander Schacht
14:30 – 15:00	*Refreshments Break*	
15:00 – 16:15	• **Estimands** ○ Problem Statement ○ ICH Working Group ○ (EFSPI) Position	Chrissie Fletcher
16:15 – 16.30	• **Idea Generation Meeting 2016**	Stefan Driessen
16:30	*2015 Meeting Closure*	

Appendix 2: **List of 26 Participants**

First	Surname	Country	Company short
Jens-Otto	Andreas	Germany	UCB
Egbert	Biesheuvel	Netherlands	Danone
Bruno	Boulanger	Belgium	Arlenda
Hans Ulrich	Burger	Switzerland	Roche
Daniele	Compagnone	Germany	AbbVie
Maylis	Coste	France	Servier
Anne	Danniau	Germany	Grünenthal
Stefan	Driessen	Netherlands	Abbott
Daniel	Evans	UK	Pfizer
Chrissie	Fletcher	UK	Amgen
Christoph	Gerlinger	Germany	Bayer
Niels Michael	Kamp	Denmark	Novo Nordisk
Olavi	Kilkku	Finland	Orion Pharma
Axel	Krebs-Brown	Netherlands	Astellas
Rosa	Lamarca	Spain	Almirall
Frank	Langer	Germany	Lilly
Inge	Leimer	Germany	Boehringer Ingelheim
Hans-Jürgen	Lomp	Germany	Boehringer Ingelheim
William	Malbecq	Belgium	MSD
Pierre	Mancini	France	Sanofi-Aventis
Roland	Marion-Gallois	France	Medtronic
Annamaria	Muraro	Italy	Chiesi
Emmanuel	Pham	UK	Ipsen
Alexander	Schacht	Germany	Lilly
Armin	Schueler	Germany	Merck
Ingrid	Sofie Harbo	Denmark	Lundbeck