EFSPI Statistics Leaders Meeting

11th June 2014

Summary and Key Messages

Executive Summary

The fifth EFSPI Statistics Leaders Meeting was held June 11, 2014, in Basel, Switzerland. A record number of thirty (30) leaders from 8 different countries and 20 pharmaceutical companies attended. After a warm welcome the meeting started with presenting EFSPI and the strategic objectives for EFSPI for 2013-2015. Also a recap of the 2013 Statistics Leaders Meeting was given including follow up actions and progress. This was exemplified by the first topic on the agenda, a follow up on the extensive discussions at the previous meeting. The Working Group (WG) on Data Sharing that was formed end of 2013 presented their objectives and informed the meeting about the current five work streams. Main goals of the group are to identify and prospectively prioritize statistical issues in data transparency, and co-ordinate and communicate on statistical contributions across Europe. The current landscape of implementation of Data Sharing in the companies was presented, including the practical issues encountered. The overview also showed that different technical solutions have been put in place by various companies.

After a short update on Special Interest Groups (SIGs) the new SIG Integrated Data Analysis presented their aims and objectives. This SIG has set up four working group dealing with Efficacy Data in phase 2 and 3, Safety Data, Network Meta-Analyses, and IDA relative to greater Data Transparency. The aspirations of the SIG were well received. The SIG was encouraged to closely collaborate with other SIGs on topics like NMA and Rare Events, and also to work on estimates for safety parameters for later use in HTA and Benefit-Risk assessments. The SIG in turn asked for case studies from the companies on certain specific areas. The Pharmaco-Epidemiology SIG were next to present their many achievements over the last 6 years of their existence with several papers, handbooks and contributions to workshops and meetings. Feedback noted benefit in revitalizing previous SIG deliverables, especially in the area of Rare Events, bias and confounding. The latter is increasingly important due to the trend of increasing observational research within Pharma.

In the afternoon in a plenary session recent developments in the industry and regulatory environment regarding data and data sciences were reviewed and discussed. All participants had received in advance pre-reads on the topics like IMI, EFPIAs New Clinical Trial Design Task Force, EMAs guidance on Parallel Scientific Advice Regulators and HTA, EMAs PAES Working Groups, and Big Data – Real World Data. Also a survey was sent out in advance on the level of involvement of the Statistics Leaders in these developing areas. They were also asked to identify present challenges and possible ways to address these. The pre-reads, the results from the survey as well as the engagement in the discussions during the meeting clearly showed that there is growing involvement and interest in these new areas of data and associated data science. Many statistical challenges were identified in performing HTA, observational studies and the use of secondary data bases and Big Data projects (even though the last item lacks a clear definition). Predominantly data quality and how to deal with bias and confounding were mentioned as challenging when working in this area. And a need for best statistical practices was voiced. Access to best statistical practices and methodologies developed by experts in the field (e.g., SIGs, working groups), will give statisticians opportunities to demonstrate their added value, by collaborating and partnering with other data scientists. In this era of electronic health records and access to large databases, big data will bring new opportunities for statisticians.

Welcome

Stefan Driessen welcomed the attendees and thanked Hans Ulrich Burger from Roche for the local organization and hosting of the meeting. A record number of thirty (30) leaders from 8 different countries and 20 pharmaceutical companies were present. The full agenda and the list of attendees is in the appendix.

EFSPI 2013-2015

Chrissie Fletcher, current President of EFSPI, explained the Statistical Leaders Meeting was initiated as a forum for Statistical Leaders to network, share ideas, shape and influence our environment and help EFSPI shape their strategy.

The EFSPI three key Strategic Objectives for 2013-2015 were presented as well as the goals for 2014 in alignment with these objectives with some of them already achieved:

1. Represent the association members of EFSPI and provide a united and respected voice on key scientific, regulatory and statistical issues in drug development
2. Enhance the profile of EFSPI in Europe and strengthen alliances and collaborations with other professional bodies within Europe
3. Set and promote professional standards in Europe for the application, understanding and communication of statistics in dug development

Recap Statistical Leaders Meeting 2013

Stefan Driessen gave a recap of the 2013 meeting and the progress on resulting actions.

The SIG Medical Devices that presented for the first time to the Statistics Leaders Meeting in 2013 was given support by EFSPI in sending a letter to EU Parliament asking for attention to introduce more profound statistical principles in the upcoming regulatory framework. Though some concerns seemed to have been taken into account the regulatory direction is different from expectations whereby the role of EMA will be less direct than expected, but on the other hand there will be less Notified Bodies than presently the case and possibly better controlled.

The Benefit-Risk SIG has made substantial progress since the presentation at the 2013 Meeting, where they were encouraged to further develop their blue print for approaching Benefit-Risk assessments by statisticians. A one-day meeting was organized September 2013 together with EFSPI and PSI, a paper reviewing key publications and initiatives on frameworks and methodologies has been submitted for publication, and collaboration with QSPI (Quantitative Sciences in the Pharmaceutical Industry) is ongoing. They are requesting companies to give their support to help organize a 2-day training course in 2015.

In the 2013 meeting special attention was given to the new topical area of Clinical Trial Data Transparency. Key messages from the Statistics Leaders were to focus on statistical principles and highlight good statistical practice on secondary (re-)analyses. Since the meeting a workshop on data sharing was organized by EFSPI/PSI and an EFSPI/PSI Working Group was formed chaired by Sally Hollis and Hans Ulrich Burger. The Working Group was asked to present progress and developments at the 2014 Meeting (see below).

Clinical Trial Data Transparency

Hans Ulrich Burger, co-chair of the Working Group (WG) on Data Sharing, presented the main objectives of the WG:

- To identify and prospectively prioritize statistical issues in data transparency
- To co-ordinate statistical contributions across Europe to the data transparency debate
- To disseminate relevant information on the topic across the statistical community
- To develop and share a vision of the potential longer term impact of data transparency

The WG wants to achieve this through the work from the following five work streams that was explained in more detail:

- Providing continuous input in EMA/EFPIA
- Recommendations for minimal analysis practices
- Future impact on biostatistics
- Minimal requirements for data sharing
- Ensuring patient data confidentiality

Christoph Gerlinger updated the attendees on the EMA policy. Since the draft policy came out many comments have been sent and there is a hot debate in the public domain. The final policy is expected to be released in July 2014. A viewpoint paper will be drafted by EFSPI following the release of the final policy.

Action: Chrissie / Christoph to co-ordinate authorship team with the Data sharing working group and the EFSPI/PSI Regulatory committee.

Rebecca Sudlow finally presented the current landscape of Data Sharing that has evolved so rapidly over the last year. She also showed the practical issues companies encountered in implementations. Different technical solutions have been put in place (or are being developed) by various companies. The model developed by GSK and to which several other companies have joined was explained in more detail. The overall impression up to now is that not very many requests for data have been actually endorsed for various reasons.

In conclusion, this area continues to evolve and it will be helpful to discuss this topic at next year's meeting.

Action: Stefan to include data transparency as a topic on next year's agenda

Special Interest Group (SIG) Update

Stefan Driessen gave a short update on the EFSPI/PSI SIGs. This year each SIG will present itself in the EFSPI Newsletter. Almost every month in 2014 a contribution from a SIG will be in the EFSPI Newsletter. Further, the SIG HTA has published several papers, and several SIGs are planning meetings for 2014 (Biomarkers, Toxicology, Modelling & Simulation, Pharmaco-Epidemiology). When more details are known this will be mentioned in the Newsletters. The newly formed SIG Integrated Data Analysis was asked to present itself in the Statistics Leaders Meeting 2014 and accepted.

Feedback noted the importance of promoting the SIGs in the new EFSPI website (under development) and in EFSPI newsletters.

Action: Chrissie to liaise with Stefan and plan SIG promotion events/opportunities relative to upcoming activities and recently completed deliverables

SIG Integrated Data Analysis

SIG Lead Byron Jones introduced the new SIG by presenting its charter:

- To form working groups to review current methodology and practice, and where necessary develop new methods or practices for the integration of data, in the following four areas:
    - Efficacy Data in Phases II and III;
    - Safety Data (maintaining links with the Epidemiology and Safety SIG);
    - Network Meta-Analysis (maintaining links with the Health Technology Assessment SIG);
    - IDAs relative to greater data transparency (maintaining links with the data transparency WG).
- To write position papers and engage in public debate by making presentations at public meetings and conferences

The four working groups have been formed in the meantime and their composition and objectives were presented. Also issues encountered by the SIG were highlighted and several questions were raised to the Statistics Leaders that stimulated the discussions and helped to get further directions for the SIG and EFSPI.

Key messages:

Feedback to SIG:

- Work with SIG Pharmaco-Epidemiology on analysis of safety data (e.g., rare events)
- Maybe good to focus on integrating data for Safety to get better estimates of events and underlying unreliability for subsequent use in, for instance, B/R and HTA
- Work with HTA SIG on NMA because it is an important topic but requires more education on statistical issues to the audience and the various stakeholders including the decision makers/takers

Action: Byron to take this feedback to the SIG for further discussion at next meeting

Request from SIG to companies:

- Are there case studies in the companies for use indicating profitable use of integrating data at the Phase 2/3 transition point?
- SIG would like to receive input in differences in reporting safety information in drug labels, within Europe or US

Action: Stat Leaders to give Byron feedback on these topics

SIG Pharmaco-Epidemiology

Jonathan Alsop, stepping in for SIG Lead George Quartey, presented the Pharmaco-Epidemiology SIG. This SIG consists of a small group of statisticians and real-world data scientists within Industry and Academia. From its formation in 2008 up to now the SIG has published several papers and presented at conferences and workshops. The SIG has also issued a Handbook on Real World Data for Statisticians. An upcoming meeting in 2014 PASS/PAES was also described . There was a rich discussion of the topic and following key messages/questions emerged.

Key messages:
Feedback to SIG:

- Does the SIG have the right connections into the other SIGs where the epidemiology could inform their work? Suggestion to touch base with specifically the Integrated Data Analysis SIG that works on analysis of rare events, distributed safety networks, and also the integrated benefit/risk.
- Is there input from this SIG into the EMA working groups on PAES guidance?
- Some critical topics that were suggested included: “Design and analysis of studies”, “Sources and evaluation of bias”, “Use of Data for Disease Understanding (not just safety)”. Suggestion to SIG to revitalize their deliverables relating to the area of bias and confounding and EFSPI could help promote their activities and help in communication

Action: Jonathan to take this feedback to the SIG for further discussion at next meeting

Feedback to EFSPI and Statistics Leaders:

- What is the overlap/bridge between the worlds of epidemiology and statistics. Should there be more of a focus on the use of epidemiological methods in clinical trials, particularly pragmatic trials and the open-label extensions to RCTs?
- Bias (confounding) is the big issue in the area so statisticians need to play their part
- Who is actually doing the work in the companies? Is it the traditional statistics groups working with epidemiology? How are companies facing up to some of the modern designs of large real world studies?
- There was a suggestion that maybe the SIG should be somewhat broader and cover the topic of Real World Data/Observational Research/Big Data/.... This is a general trend in the industry and EFSPI/statisticians should contribute but would also be in need for proper training to de-risk credibility issues

Action: Stefan to follow up with George Quartey if it would be useful to have more statisticians join the SIG and be champions for other statisticians to engage in this area.

Involvement in Recent Developments in Data and Data Science

Recent Developments

In the afternoon in a plenary session the recent developments in the data area and data science were reviewed and discussed. Chrissie Fletcher presented briefly the array of initiatives, new guidelines and/or working groups. All participants had received in advance pre-reads on these topics:

- IMI: GetReal, IMI2
- EFPIA: New Clinical Trial Design Task Force
- EMAs Parallel Scientific Advice Regulators + HTA
- EMA PAES Working Groups
- Big Data – Real World Data

Many companies are involved in IMI projects. This includes company statisticians when it comes to improving study design and processes, though this may be less visible to the stats community as a whole. Innovations in clinical trial designs and methodologies to assess treatment effects including Benefit Risk assessment has been defined as major axis of research, where statisticians can contribute. This extends to data coming from pragmatic trials and other observational studies whereby the focus will be on establishing relative effectiveness.

The shift to addressing challenges in society, including real life medical practice is also apparent from the draft guideline on EMA-HTA parallel scientific advice and from the initiative to come to a guidance on so-called Post Approval Efficacy Studies (PAES). The latter can comprise of observational studies such as registries, pragmatic trials and use of secondary, health record, data bases.

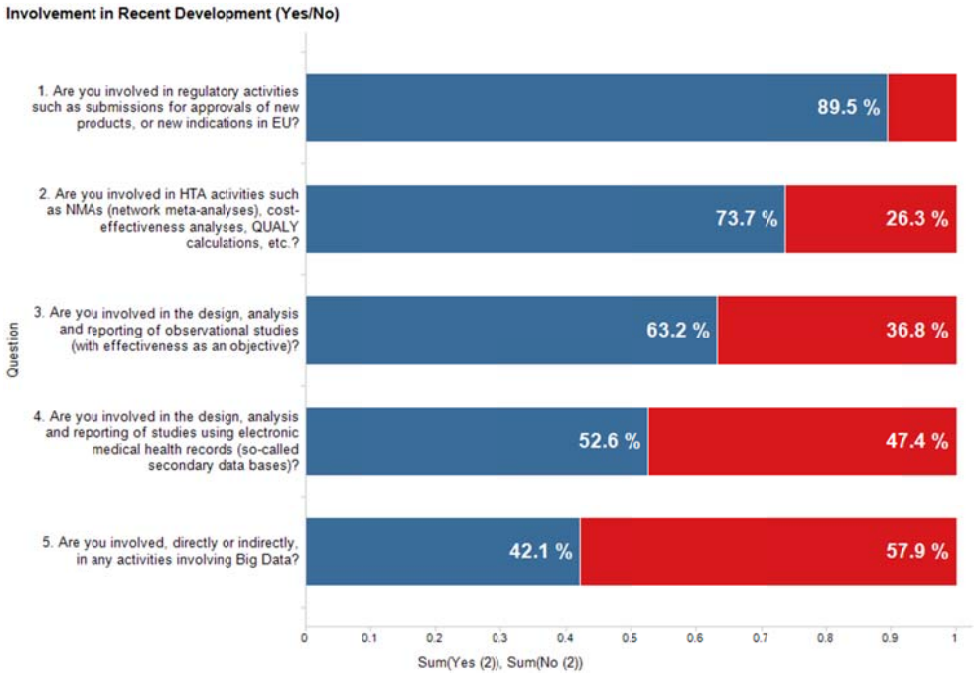
Feedback:

- All these developments will bring about new sources of data and methodologies that also the statisticians can and maybe should play their part.
- Use Statistics Leaders mailing list to disseminate regularly interesting/important info on these matters
- EFSPI/PSI regulatory committee to set up PAES working group to be prepared for giving comments on the upcoming guidance, especially on use of pragmatic trials and observational studies (begin work now on identifying the various statistical issues whilst the guideline is being written) – seek to partner with the EFPIA PAES working group via Chrissie Fletcher

Action: Chrissie to follow up with Lesley France (chair of EFSPI/PSI regulatory committee) to set up PAES working group.

Survey on current Involvement

In order to assess this shift and the extent to which the companies' statistical units in Europe are involved and to further know about their challenges and needs a survey was sent out to the participants out of the group of Statistics Leaders. The response rate was 61% (19/31). .



Take home messages from the survey were:

- of those that responded a decreasing level of involvement is currently present when the topic at hand can be judged as being more distant from the more regulatory area of RCTs (see Table)
- many statistical challenges in these (new) areas:
    - HTA (validity NMAs, treatment switchers, subgroup analyses, quantifying uncertainty in effects and cost outcomes, differences between HTAs in preferred methodology)
    - observational studies (bias, confounding, missing data, quality of data, combining efficacy and real world effectiveness)
    - secondary data bases (suitability because there are many, quality of data: much missing data, and what is actually measured/represented)
    - Big Data (same as with secondary databases), but as important: what is Big Data? A proper definition would help to better understand this emerging area
- the statistician can and should play a part in these new developments
    - by trying to get a seat at the table, and
    - demonstrating added value through access to best statistical practices and methodologies developed by the field (e.g., SIGs, working groups).

Plenary Discussion

Stefan Driessen presented the results of the survey and Chrissie Fletcher chaired the discussion on what the Statistics Leaders would see as priorities for EFSPI to focus on. Also the kind of involvement that they would like to see from EFSPI was queried.

Key messages from the session were

HTA:

- identify examples to make the case that statistics/statisticians can bring added value to the HTA discussions; this could help others to get a seat at the table
- Sharing of best practice implementations (via SIGs)
- Collaborate with medics and economitricians active in this area
- Address the need of experience and expertise in HTA by supporting training programs (Note: PSI is preparing HTA course for 2015 with help from HTA SIG)
- Certain companies indicated that there is a growing role for statisticians in HTA ((NMA, modelling, etc.)
- Stat Leaders need to champion the engagement of statisticians in HTA activities within their companies

Action: Chrissie to take this feedback to the HTA SIG for further discussion at their next meeting. The HTA SIG will loop back to the Stat Leaders community for ideas of how they can best champion role of statisticians in HTA

Observational Studies:

- Address need for experience and expertise in observational studies and the big issue of bias and confounding
- Develop/dissiminate handbook (via SIG)
- Possibility to develop eLearning modular course with support from EPI SIG
- Stat Leaders need to champion the engagement of statisticians in observational research within their companies

Action: Jonathan to take this feedback back to the EPI SIG for further discussion at their next meeting

Secondary data

- Same need for training on issue of bias and confounding
- Many questions on operational issues (data cleaning)
- Links to pragmatic trials as electronic health records can help design these trials
- EPI SIG could develop position paper highlighting the value for why statisticians need to understand secondary data sources

Action: Jonathan to take this feedback back to the EPI SIG for further discussion at their next meeting

Big Data

- Need for proper definition of “Big Data”
- Need to think about what is coming up and the right statistics for this kind of data
- Maybe set up of small working group (which could become a big data SIG) with a clearly pre-defined “problem to tackle”, for instance, how to deal with the upcoming stream of data captured and real-time transmitted through smartphones, apps and/or wearables.
- Can Stat leaders share experiences of big data strategies relative to role of statistics at next years meeting?
- Seek to partner/collaborate with other expert/specialist areas e.g. data mining

Action: Stefan to ask Stats Leaders for volunteers to set up small working group on Big Data and suggestions for other groups/organisations to partner with

Appendix 1: **AGENDA Statistical Leaders Meeting 2014**

Wednesday June 11, 2014
Basel, Switzerland
Roche facilities

Time	Topic	Presenter / Facilitator
9:00 - 9:30	• **Welcome address + Intro** o Org. Ctee o EFSPI President o Recap Stats Leaders meeting 2013	Stefan Driessen + Hans Ulrich Burger Chrissie Fletcher Stefan Driessen
9:30 - 11:00	• **Clinical Trial Data Transparency** o Update by Working Group o EMA - Latest Developments o Practicalities of Data Sharing	Hans Ulrich Burger Christoph Gerlinger Rebecca Sudlow
11:00 - 11:30	*Break*	
11:30 – 12:15	• **SIGs – Update** • **SIG Integrated Data Analysis** o Introduction + Discussion	Stefan Driessen Byron Jones
12:15 - 13:00	• **SIG Pharmaco-Epidemiology** o Introduction + Discussion	Jonathan Alsop
13:00-14:00	*Lunch break*	

Time	Topic	Presenter / Facilitator
14:00 - 15:00	• **Recent Data & Design Developments:** o **IMI: GetReal, IMI2** o **EFPIA: New Clinical Trial Design Task Force** o **EMAs Parallel Scientific Advice Regulators + HTA** o **EMA PAES Working Groups** o **Big Data – Real World Data**	Round Table Discussion: Chrissie Fletcher Stefan Driessen Uli Burger
15:00-15:15	*Break*	
15:15 – 16.15	• **Recent Developments - continued**	
16:15 – 16.30	• **Meeting summary**	Stefan Driessen
16:30	*Meeting adjourn*	

Appendix 2: List of 30 Participants

First Name	Surname	Affiliation	Country	Affiliation type
François	Aubin	Cardinal Systems	France	CRO
Paul	Fardy	CROS NT	UK	CRO
Kevin	Carroll	KJC Statistics	UK	CRO
Jonathan	Alsop	Numerus Ltd.	UK	CRO
Andrew	Garrett	Quintiles	UK	CRO
Michael	O'Kelly	Quintiles	UK	CRO
Stefan	Driessen	Abbott	The Netherlands	Pharma company
Chrissie	Fletcher	Amgen	UK	Pharma company
Josie	Wolfram	Astellas	The Netherlands	Pharma company
Christoph	Gerlinger	Bayer	Germany	Pharma company
Thorkild	Nielsen	Bayer	Germany	Pharma company
Torsten	Westermeier	Bayer	Germany	Pharma company
Hans-Jürgen	Lomp	Boehringer Ingelheim	Germany	Pharma company
Giacomo	Mordenti	Grünenthal	Germany	Pharma company
Sara	Hughes	GSK	UK	Pharma company
Andrew	Roddam	GSK	UK	Pharma company
John	Whittaker	GSK	UK	Pharma company
David	Morgan	Ipsen	UK	Pharma company
Frank	Langer	Lilly	Germany	Pharma company
Ingrid	Sofie Harbo	Lundbeck	Denmark	Pharma company
Roland	Marion-Gallois	Medtronic	France	Pharma company
Armin	Schueler	Merck	Germany	Pharma company
William	Malbecq	MSD	Belgium	Pharma company
Byron	Jones	Novartis	Switzerland	Pharma company
Niels Michael	Kamp	Novo Nordisk	Denmark	Pharma company
Olavi	Kilkku	Orion Pharma	Finland	Pharma company
Hans Ulrich	Burger	Roche	Switzerland	Pharma company
Sylvain	Nicolas	Sanofi	France	Pharma company
Maylis	Coste	Servier	France	Pharma company
Jens-Otto	Andreas	UCB	Germany	Pharma company