European Federation of Statisticians in the Pharmaceutical Industry

Representing Statistical Associations in Europe

EFSPI Annual Report 2018

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Authors: Chrissie Fletcher

Hans Ulrich Burger

Birgitte Biilmann Rønn

Christoph Gerlinger

Egbert Biesheuvel

Justine Rochon

Maylis Coste

Julie Mellish

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Highlights from the EFSPI President & Vice President

2018 was a very busy year, probably for every one of us, for me personally, but also for EFSPI as an organization. It was the first year of my two year tenure as president, a lot of activities were ongoing in 2018 and some of them were really important for the organization.

As every year we organized a number of seminars and workshops to support scientific discussions in our communities. 2018 we had a workshop in March on Recent Advances in Clinical Trials jointly with the PSDM hosted by Astellas in Leiden, we had a workshop on Small Populations together with the BBS in Basel in June, hosted by Idorsia, and finally as a last event we had a workshop on Decision Making in Drug Development in December, hosted by Servier in Suresnes. And finally we were able to hold the third annual EFSPI regulatory statistics workshop in Basel. Especially the annual regulatory statistics workshop is really important specifically for us as it brings EU regulators and industry together to discuss important topics relevant for both sites. Importantly, the workshop is organized by a joint committee from both sites, EU regulators and industry representatives to ensure that important topics from both sides are discussed in the workshop. Of note, this year also Rajeshwari Sridhara from FDA joined the conference. It takes a lot of energy to organize such a workshop, from everyone in the scientific committee and the local organization committee and especially from the chair person. This year the chairperson role was very successfully taken up by Kaspar Rufibach. Many thanks to Kaspar and everyone on the scientific organizing and the local organizing committees for this event! And many thanks to Egbert Biesheuvel for organizing and aligning all these seminar and workshop activities.

We had this year also the 9th statistics leaders meeting hosted by Arlenda at Louvain-la-Neuve on July 12th. We brought again about 30 industry leaders together to discuss important topics. More information can be found on the EFSPI web. After the first 8 statistics leaders meetings have been organized by Stefan Driessen this was the first one organized by Justine Rochon. It was great to see that because of a great handover we were able to maintain continuity of this meeting on one hand whilst being able to bring new elements in on the other hand. Many thanks to Justine and Stefan for another very successful meeting and a very successful handover!

Another important scientific element of EFSPI are the SIGs, i.e. the scientific interest groups, in which everyone across Europe can get engaged in an important topic. We share most of

the SIGs together with PSI which makes a lot of sense for attracting as many colleagues as possible. Also for the SIGs we had a successful handover this year from Stefan Driessen to Maylis Coste and Anne Danniau. Thanks again to Stefan for all his work on this beforehand and to Maylis and Anne to take on this important activity. Of note, this year we also saw three new SIGs getting approved, one on the use of historic control data and two on the use of estimands in Neuroscience and Oncology.

There were also a lot of important "administrative" activities this year to finish. Most importantly, we became a registered association in Denmark. This is very important for us as an organization as it allows us to officially participate in EU projects. The registration was not straightforward as we are not a usual association of members but of member organizations only. Originally we thought to register in UK but Brexit really interfered with that as we wanted to be an EU registered organization. After a lot of discussions we found out that Denmark would be the best country for registration. Denmark however demanded to define a local role of a director in Denmark to cope with the Danish law; I am happy to report that Mette Krog Josiassen accepted this role. Many thanks to her! As a consequence we also had to adopt the constitution of EFSPI. An update can be found on the EFSPI webpage. Finally, as a registered organization we were also affected by the new EU's General Data Protection Regulation (GDPR); and we needed to define a new corresponding policy which is now also available on the EFSPI webpage. Many thanks to everyone involved in these really important activities!

Finally, running successfully an organization like EFSPI goes much beyond the capacity of one individual. I am very fortunate to have a very active EFSPI council beside me and I am grateful for all the help I have received from my colleagues on the council and would like to thank every council member for all the support. Specially, I would like to thank Marisa Bacchi as vice president, Birgitte Biilmann-Roenn as treasurer and Christoph Gerlinger, Egbert Biesheuvel and Chrissie Fletcher for their countless activities.

We are now looking forward to 2019 to be another successful year for EFSPI. We have already started to organize this year's scientific meetings, especially the next EFSPI regulatory statistics workshop. It will take place on September 23/24th 2019, one more time in Basel. For 2020 it is planned to move it to Amsterdam area 2020 to be closer to the EMA. I am very confident that we will have this year again an attractive program leading to great discussions! And it would be great to see again a lot of colleagues from all over Europe to join the meeting!

We will continue to keep you informed about all the news in our monthly EFSPI newsletters.

Hans Ulrich Burger (Switzerland)

President

Finance

The financial situation was again stable in this year. The income was primarily driven by the statistics leaders meeting, the scientific meetings and the regulatory statistics workshop and has put the organization into a comfortable situation for the next years. The same activities, the statistics leaders meeting, the scientific meetings and the regulatory workshop also drove the main expenses. Noticeable, the executive office hours were well inline with what we had predicted beginning of the year. The current overall balance continues to be solid and is a good basis for upcoming years. (Hans Ulrich Burger on behalf of Birgitte Biilmann Rønn)

EFSPI Income and Expenses 2018 - UPDATE

	Actual €	**Budget €**	Variance €
Income			
Membership Fees	12,250	12,250	0
Scientific Meetings	23,210	17,000	6,210
EFSPI Statistics Leaders Meeting	6,450	6,000	450
EFSPI Regulatory Statistics Workshop	45,800	30,500	15,300
Recruitment Web Advertisement	2,450	1,400	1,050
Other Income	1.080	0	1,080
	91,240	67,150	24,090
Expenses			
Executive Office Hours	13,962	15,840	1,878
Attending Meetings	0	450	450
Web Development & Hosting	750	940	190
Office Costs	874	1,200	326
Bank Charges	464	2,000	1,536
Scientific Meetings	9,022	10,000	978
EFSPI Statistics Leaders Meeting	1,193	2,000	807
EFSPI Regulatory Statistics Workshop	30,414	23,000	(7,414)
EFSPI Incorporation	1,199	1,500	301
Anticipated revenue sharing	4,679	0	(4,679)
	62,554	56,930	(5,624)
Net result for the year	28,686	10,220	18,466

Balance

	2018 €	2017 €
Current assets		
Debtors	33,785	9,185
Sundry debtors	239	239
Prepayments	-	72
Accrued Income	-	13,895
Bank - €	106,906	84,502
Bank - £ (Converted to €)	2,550	5,588
	143,480	113,481
Current liabilities		
Creditors	8,962	10,006
Accruals	5,619	3,262
	14,581	13,268
Revenue reserves		
Balance brought forward	100,213	70,211
Result for year to date	28,686	30,002
	128,899	100,213

Hans Ulrich Burger on behalf of
Birgitte Biilmann Rønn (Denmark)

EFSPI Treasurer

EFSPI Regulatory Statistics Workshop



On the 24th and 25th September the 3rd EFSPI Regulatory Statistics Workshop took place in Basel. With over 260 registrations (up >60 from last year) the turnout was again excellent. A few highlights include:

- Attendance of industry, academic, and regulatory colleagues, with engaged discussion on a broad range of topics relevant to contemporary drug development.
- An asset of the workshop is how approachable regulators are, on and off stage. And they do not shy away from pronounced statements, e.g. in panel discussions.

A few quotes heard at the workshop:

- Benjamin Hofner (PEI): *Regulators are generally open for innovative topics (e.g. platform, basket, umbrella, RWE) – but go and discuss with them early!*
- Anja Schiele, Senior Statistical Advisor NOMA, chair EMA BSWP. *Resistance to single-arm trials is even larger for HTA bodies than for regulators. We prefer an underpowered RCT to a single-arm trial.*
- Rob Hemmings (MHRA): *Randomisation is (really, really) important, isn't it? Did something change? Quality of evidence is paramount. Limited scope for trade off in quality vs. cost. Is supplementing with external data conceivable? Perhaps. Commonly? No. Do not pretend it is easy to use RWD: Use three covariates for PS modelling and you are done does not work.*
- James Roger (LSHTM): *ICH E9 will drive Cox regression out of business!*

The materials from the workshop are stored on the website (www.efspi.org).

Hans Ulrich Berger Egbert Biesheuvel Christoph Gerlinger

Members of the EFSPI Regulatory Statistics Workshop planning team

Regulatory Affairs

Objectives

The role of the regulatory committee is to provide the EFSPI/PSI viewpoint on regulatory issues. This includes promoting best practice, reviewing regulatory policy and guidelines, driving debate on future guidance, and engaging with statisticians in European regulatory agencies.

General

During 2018 the regulatory committee held five regular committee meetings, as well as meetings with the EMA's Biostatistics Working Party (BSWP) and the MHRA statisticians. The committee coordinated the review of several regulatory guidance documents (more detail below). Committee members have contributed to EMA and industry workshops, as well as webinars, on topics such as estimands, clinical trial transparency, and PROs. In addition; members of the committee helped organize the 3rd EFSPI workshop on regulatory statistics held in Basel as well as two plenary sessions at the PSI conference in Amsterdam (the regulatory town hall and an estimand role play).

In July the chair of the regulatory committee transferred to Anna Berglind from Christoph Gerlinger, who is now the co-chair of the committee.

Expert Groups

Two regulatory expert working groups were active at the beginning of 2018: the expert group on subgroups continued the work on developing a best practice for subgroup analyses and published a paper on the topic in Pharmaceutical Statistics (1). This expert group is still active. In addition, the expert group on confidentiality of interim results established following the 2016 meeting with the BSWP was still active at the beginning of the year. The committee agreed at the committee meeting in September 2018 to pause the work in this expert group following finalizing the slides and minutes from the BSWP-meeting 2017 in which the recommendations from the group are documented.

(1) Dane A, Spencer A, Rosenkranz G, Lipkovich I, Parke T, on behalf of the EFSPI/PSI Working Group on Subgroup Analysis. Subgroup analysis and interpretation for phase 3 confirmatory trials: White paper of the EFSPI/PSI working group on subgroup analysis. Pharmaceutical Statistics. 2018;1–14. https://doi.org/10.1002/pst.1919

Meetings with statisticians from regulatory agencies

On September 19, 2018, the EFSPI/PSI regulatory regulatory committee met with the MHRA statisticians in London. Topics discussed included: the use of historical / dynamic borrowing / synthetic control arms for regulatory decision making, innovative study designs, quality tolerance limits and risk based monitoring, estimands, protocols for device (non-drug) studies, statistical assessment of quality attributes, treatment switching in oncology, parametric modelling for estimation of treatment benefit in survival analyses, the increase in innovative adaptive designs to evaluate biomarkers, how to analyse multiple occurrences of hospitalization in CV trials, the use of trimmed means to handle missing data, and CRF standards for reason for withdrawals.

In addition, the regulatory committee met with the EMA's BSWP on October 8, 2018. Topics discussed included: implications of EMA's Brexit preparedness business continuity plan on statistics, use of external ("real world") evidence in confirmatory studies, and sharing blinded data of an ongoing study.

Guidelines

The regulatory committee collated comments on the following documents during the year:

- FDA's draft guidance on Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics; draft Guidance for Industry (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621817.pdf)
- FDA's draft guidance on Adaptive Designs for Clinical Trials of Drugs and Biologics; draft guidance for industry (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf)
- FDA's draft guidance on Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products Guidance for Industry (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM625241.pdf)

- FDA's draft guidance on Presenting Quantitative Efficacy and Risk Information in Direct-to-Consumer Promotional Labeling and Advertisements Guidance for Industry (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM623515.pdf)
- EMA's draft Questions and Answers on Data Monitoring Committees issues (https://www.ema.europa.eu/documents/scientific-guideline/draft-questions-answers-data-monitoring-committees-issues_en.pdf)

Special thanks to Anne Danniau, Jürgen Hummel, Tony Sabin and Kaspar Rufibach for collating comments for the committee.

Also, special thanks to Anna Berglind for writing this annual report.

Christoph Gerlinger (Germany)

Regulatory Chair

Scientific Affairs

The Scientific Committee organised three successful 1-day scientific events in Europe in 2018:

1. The 1st one was a joined EFSPI / PSDM event on '**Recent Advances in Clinical Trial Design**', in the Netherlands on 23rd of March hosted by Astellas. This meeting offered participants to interact with speakers from academia, regulatory agencies and industry on recent developments in designing clinical trials. With almost 70 attendees and high-quality presentations it has been a very successful event. In particular the pilot of the first formal debate was a successful exercise on the motion:

   "This house believes the arrival of Big Data makes controlled clinical trials obsolete"

   Slides of the presentations can be found here https://www.efspi.org/EFSPI/Events/Archive_Items/Recent_advances_in_Clinical_Trials.aspx

2. The 2nd 1-day meeting on '**Small populations and level of evidence**' took place on 27th of June at Idorsia near Basel. This meeting was organised by the BBS and EFSPI, and discussed latest development of methods in small populations among experts from regulatory bodies and practitioners from pharma and academia. A very well attended meeting with more than 100 delegates.

   The presentations of this meeting can be found at the EFSPI homepage under 'Past Events' https://www.efspi.org/EFSPI/Events/Archive_Items/Small_populations_and_level_of_evidence.aspx

3. The 3rd one was a scientific meeting on '**Decision making in Clinical Development**', which took place on 12th of December hosted by Servier in Paris. Taking decisions during the development of a new drug requires combining many and varying pieces of information. Decision-makers need quantitative tools to support informed decisions, with transparent processes that synthesize the whole available information in order to evaluate the success associated to different options. Besides presentations, this meeting offered poster presentations as an additional feature.

   Slides of the presentations as well as posters of this successful event are available on our website

https://www.efspi.org/EFSPI/Events/Archive_Items/Decision_making_in_drug_development.aspx

In 2018, the Scientific Committee consisted of the following members:

- Francois Aubin (Venn Life Sciences, France)
- Egbert Biesheuvel (Nutricia Research, Netherlands) - Chair
- Alexandra Green (consultant, UK)
- Axel Krebs-Brown (Merck, Germany)
- Emmanuel Quinaux (IDDI, Belgium)
- Pierre Verweij (Idorsia, Switzerland)
- David Wright (Astra Zeneca, UK)
- Julie Mellish (KSAM, UK) – Administration

Egbert Biesheuvel (the Netherlands)

Scientific Chair

Statistics Leaders Meeting

On 12-July 2018, the 9th EFSPI Statistics Leaders meeting took place in Louvain-la-Neuve, Belgium. EFSPI leadership meetings are key for shaping the future strategy of the European Federation of Statisticians in the Pharmaceutical Industry. This year's meeting was an event with 30 participants from more than 20 companies. A strong community and network has emerged over time within the Statistical Leaders based in Europe. Agenda topics included updates from EFSPI, training, management of SIGs, Bayes statistics and an afternoon workshop on pragmatic trials and external controls.

Regarding training, the EFSPI statistics leaders confirmed the need for more training and also recommended EFSPI take a leadership position. A new role assigned to oversee training will be discussed at the next EFSPI Council meeting. Key activities should include promotion of important training topics and a coordination with member organizations, including technical and soft skills training, and training for future leaders.

Regarding SIGs, the quantitative decision making SIG provided a summary of all their accomplishments since the SIG began in Q4 2017 (see SIG update below for more details). The commitment of all the SIG Chairs and all individuals participating in the SIGs was appreciated and commended by all the EFSPI Statistics Leaders. Within EFSPI the SIGs will now be managed by Maylis Coste (Servier) and Anne Danniau (Grunenthal).

Regarding Bayes statistics, EFSPI were recommended to provide a platform with regulatory statisticians to enable wide discussion across the EU Statistics community on the use of Bayesian approaches supporting drug development. In addition, non-statisticians will need training and EFSPI could help facilitate this.

The afternoon workshop was a big success. Participants liked it both for its contents and its new Agile format which was a combination of Story Mapping and World Café. We spent a few hours to create a shared understanding among the participants regarding open questions, challenges, risks, and potential EFSPI follow-up activities on pragmatic trials and external controls.

All material from the EU Statistics Leaders Meetings is available on the EFSPI website:

https://www.efspi.org/

Justine Rochon (Germany)

Statistics Leader Forum Chair

Special Interest Groups

Over 2018, SIGs for multiple companies expressed their dynamism as working groups involving Statisticians open-minded and ready to share and contribute. Their activity has been shared through publications, webinars, participation to conference, presentations to Statistical leader meeting. On the other end, to increase the SIGs visibility, align information presented in EFSPI and PSI websites and facilitate access to their reports and deliverables, jointly EFSPI and PSI decided to structure the SIGs oversight: A. Crisp (PSI) and A. Danniau and M. Coste (EFSPI) contributed to that objective .

The list all the SIGs active in 2018 is provided below:

Biomarker (leader = Athula Herath, heratha@MedImmune.com)

Benefit-risk (leader = Alexander Schacht, schacht_alexander@lilly.com)

Health Technology Assessment, HTA (leader = Chrissie Fletcher, fletcher@amgen.com)

Integrated Data Analysis (leader = Byron Jones, byron.jones@novartis.com)

Medical Devices (leader = Martin Wadepuhl, wadepuhl.m.vsa@t-online.de)

Modelling & Simulation (leader = Chris Campbell, ccampbell@mango-solutions.com)

Real World data (leader = Maurille, maurille@amgen.com)

Toxicology (leader = Gareth Thomas, ThomasG@UKOrg.Huntingdon.com)

Small Populations (leader = Egbert Biesheuvel, egbert.biesheuvel@danone.com)

AIMS (leader = Craig McIlloney, craig.mcilloney@ppdi.com)

Quantitative Decision-making support (leader: Gaelle Saint-Hilary, gaelle.saint-hilary@servier.com, Pierre Colin, Pierre.Colin@sanofi.com)

Maylis Coste (France)

Servier Group

Communications

Monthly newsletters were distributed in 2018. Key highlights announced during the year included local association news and upcoming events.

All newsletters are available on the EFSPI website (www.efspi.org).

Chrissie Fletcher (UK)
Communication Officer

Operations Board Summary

The Operations Board had monthly teleconference meetings over the year, during which all ongoing and future activities were reviewed and issues discussed.

The board is composed of: Marisa Bacchi (Vice-President), Hans Ulrich Burger (President), Birgitte Biilmann Rønn (Treasurer), Egbert Biesheuvel (Scientific Affairs), Justine Rochon (Statistical Leaders Meeting), Maylis Coste (SIGs), Chrissie Fletcher (Communications Officer), Christoph Gerlinger (Regulatory Affairs), and Julie Mellish (Executive Office).

Council Membership

In 2018, 10 countries national associations of pharmaceutical statisticians from 10 European countries were represented within EFSPI, totalising a combined membership of more than 2200.

Members of the EFPSI Council at the end of 2018 are listed in the Appendix.

Council Summary

Two Council meetings were held in 2018. In addition to the two face to face meetings, two web conferences were held.

Executive Office

The Executive Office facility continues to be provided by Kingston Smith (UK). Julie Mellish is the Secretariat for EFSPI.

Appendix: Council members at the end of 2018

Belgium
Emmanuel Quinnaux, IDDI
An Vandenbosch, Janssen

Denmark
Mette Krog Josiassen, Lundbeck
Birgitte Biilmann Rønn, Novo Nordisk

Finland
Sami Virtanen, Orion Pharma
Teppo Huttunen, 4Pharma

France
Emmanuel Pham, Ispen
Maylis Coste, Servier

Germany
Justine Rochon, Boehringer Ingelheim
Christoph Gerlinger, Bayer

Italy
Fabio Montanaro, Latis
Marco Costantini, GSK

Netherlands
Stefan Driessen, Abbott
Egbert Biesheuvel, MSD

Sweden
Mattis Gottlow, AstraZeneca
Anna Ekman, AstraZeneca

Switzerland
Hans Ulrich Burger, Hoffmann-La Roche
Marisa Bacchi, Idorsia

UK
Chrissie Fletcher, Amgen
Ray Harris, Eisai