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

EFSPI Newsletter

NOVEMBER / DECEMBER 2022

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WELCOME

A warm welcome to the winter 2022 edition of our EFSPI newsletter!

It is end of year, the winter solstice is approaching, festive decorations are all over the places, and it is time to slow down and reflect.

After another unprecedented year in which we have somehow learned to live with the pandemic but in which 2022 taught us that war in Europe is no longer unthinkable, and global warming has an impact on all ecosystems and we put the future of next generations at stake if we continue to do business as usual, I want to gratefully acknowledge the truly collaborative work within EFSPI.

This special edition is simply dedicated to people who care about other people.

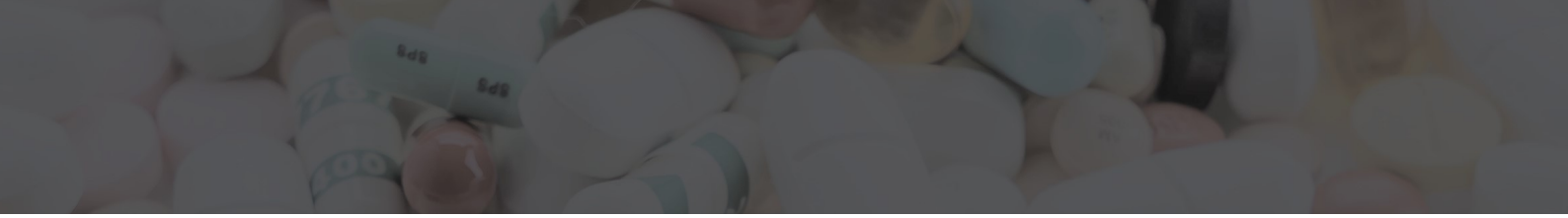
It highlights some of our greatest achievements as a community and provides insights into key drivers of our current and future success. This success is the result of a lot of hard work of people who are enthusiastic about data and statistics, and who understand how important our profession is to society, and how our work impacts people's lives. Enjoy the reading and let me know how you liked this special edition.

Stay healthy, stay safe wherever you are!

Justine Rochon
EFSPI President and
Editor of EFSPI Newsletters

EFSPI COUNCIL NEWS Save the date!

The 8th EFSPI Regulatory Statistics Workshop will take place at the Biozentrum in Basel on 13–14 September 2023.



Personnel Update

Getting to know Helle Lynggaard

Please join us in welcoming Helle Lynggaard as new chair of EFSPI Regulatory Statistics Workshop. In this role, Helle will chair the workshop's Local Organizing Committee with representatives from industry. This committee is responsible for logistics and for forming the Scientific Committee. In addition, she will chair the Scientific Committee and will work together with representatives from regulatory agencies, industry and academia to prepare the scientific content of the workshop.

These are big shoes to fill as Kaspar Rufibach has done in this role such a wonderful job. A big, big thank you to Kaspar for what he all accomplished in the past and all the best and plenty of success for Helle in her new role. Helle, you will rock it!

Helle Lynggaard is a Principal Statistician at Novo Nordisk, based in Copenhagen/Denmark. She has 25+ years of experience in the pharmaceutical industry working in different roles. Currently, she holds the subject matter expert role on estimands in Novo Nordisk. Helle is passionate about cross-company collaboration. In 2018, she joined the TransCelerate BioPharma Inc. collaboration on Clinical Template Suite. In 2019, she became member of the EFPIA and EFSPI co-sponsored Estimand Implementation Working Group (EIWG), where she leads one of the sub-teams.

5th EFSPI Council Meeting 2022

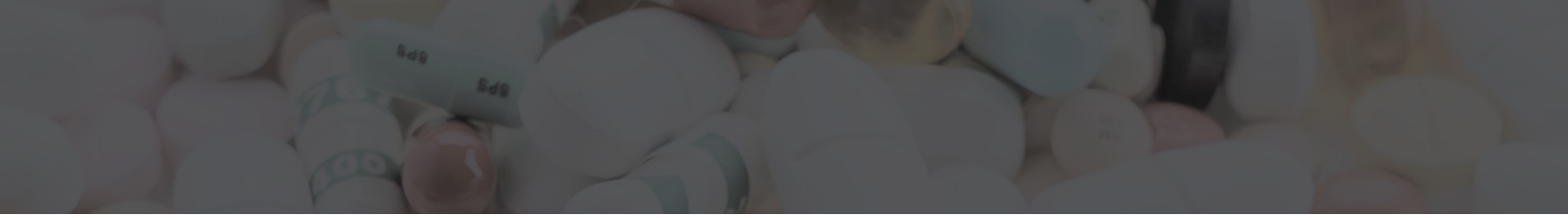
The EFSPI Council met in December for the last time this year. The main topic of this fully virtual meeting was the future location of our EFSPI office, its services to the member associations and the broader EFSPI community, including a more user-friendly version of our website. In addition, we did a final reflection on how far we have come regarding our EFSPI priorities.

What have been our priorities? You might remember that we wanted to FOCUS on ensuring business continuity, to ENHANCE our branding and visibility, and to further TRANSFORM EFSPI into a federation that makes a difference today and in the future by engaging with key stakeholders.

Our key takeaway from our 2022 retrospective was that EFSPI not only 'survived' the pandemic but became even more strategic and future-oriented. What we did very well was to keep focus and make sure that our core business continues to grow. The most prominent examples here are the very successful EFSPI events, especially the 13th EFSPI Statistical Leaders Meeting in July and the 7th EFSPI Regulatory Statistics Workshop in September. We also intensified our interactions with the statistical associations in Europe that are under the umbrella of EFSPI and helped them to promote their local activities. Last but not least, we continued to support the European Special Interest Groups (ESIGs) making their important work even more visible, and we have established a foundation for EFSPI's Training Academy.

We must admit that we did not manage to improve our EFSPI website in 2022 which is a big pain point for many users. However, the new website turned out to be a bigger endeavour and investment than we had originally thought. It will take us a while to fix the current gaps and become more user-friendly. We therefore ask you for your patience. On the positive side, we have managed to increase our presence on LinkedIn. When we look at our followers, the EFSPI community has grown faster than we could have ever imagined. In addition, we introduced a new format of our newsletters. And, this in turn, seems to enable us to have a bigger impact: One special highlight of 2022 was that EFSPI is now considered a key stakeholder and was invited as such to the table by EMA. We also had several interactions with EFPIA and are confident that this exchange will greatly enrich both sides. In addition, we felt honoured to be invited to Biostatistics Leadership Consortium (BSLC) and to DIA's Statistics and Data Science Community Core Committee meetings to present our federation of statistical associations in Europe to organizations in the USA and initiate a dialogue on future collaboration.

The EFSPI Council wants to thank you all for a truly collaborative year 2022! Please keep on supporting us by providing constructive feedback, generating ideas that fit into our EFSPI vision and eventually translating them into practice. We are committed to serve at our best our community needs and make consistent progress, one step after another.



EFPIA / EFSPI ESTIMAND IMPLEMENTATION WORKING GROUP (EIWG)

efpia
European Federation of Pharmaceutical Industries and Associations

EFSPI
EUROPEAN FEDERATION OF STATISTICIANS IN THE PHARMACEUTICAL INDUSTRY
Representing Statistical Associations in Europe

"EIWG brings together statisticians and clinicians to support the estimand journey"

EIWG Scope & Setup

To provide a cross-industry forum to:

- Share Industry and Academic experiences of implementing the new estimand framework introduced in ICH E9(R1)
- Discuss issues emerging through implementation
- Be champions and engage in scientific discussion about the value and benefits of the framework

With the aim to:

- Give feedback and recommendations for best practices
- Promote broad understanding and awareness of the framework within and outside of statistics
- Consolidate issues and topics for discussion with the ICH E9 Implementation Working Group

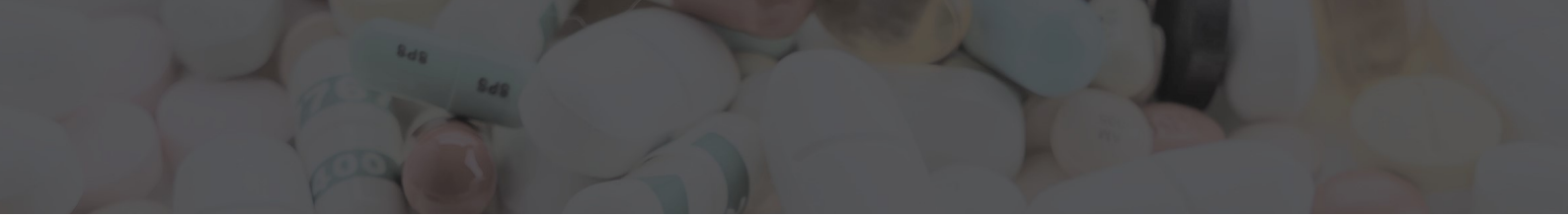
EIWG is set up to be diverse and inclusive when it comes to companies' representation. Currently 59 members represent 32 companies and institutions.

EIWG Structure & Topics

The EIWG is co-lead by Amel Besseghir, Chrissie Fletcher and Nanco Hefting. The working group is operating in seven sub-teams.

The most recent sub-team focuses on late phase and on the impact of estimands in Health Technology Assessment (HTA) and Real World Evidence (RWE).

- **Training sub-team**
  - Lead: Judith Anzures-Cabrera
- **Estimation sub-team**
  - Lead: James Bell
- **Reporting estimands**
  - Lead: Melanie Wright
- **Early Phase & Other Studies**
  - Lead: Sue McKendrick
- **Estimands in late phase**
  - Lead: Pepa Polavieja and Antonia Morga
- **Estimands in non-inferiority trials**
  - Lead: Helle Lynggaard
- **Communications**
  - Lead: Stefan Englert



EIWG Achievements 2022

Training sub-team

The training committee has continued to work on webinars for their training series 'EIWG Estimand Training Academy' targeting anyone working in clinical trials.
All trainings provided so far are freely available as 'Video-on-Demand'
Portal: https://psiweb.org/vod/Index/
or YouTube on the EFPIA channel

Estimation sub-team

Estimating the treatment-policy strategy with continuous data and incomplete post-intercurrent event (IE) follow-up is a relevant and under-researched issue. To address it, the group has assessed the performance of different estimators – based on either multiple imputation (MI) or mixed effect models (MMRM) – for simulated trials based on the HbA1c endpoint from the PIONEER1 study.
The properties of the estimators (bias and variance shown here) generally confirm the equivalence of MI and MMRM approaches (if the same assumptions are made) and the particular importance of collecting post-IE data. The complex trade-off between variance inflation and accuracy needs to be carefully evaluated further.

Early Phase & Other Studies sub-team

This sub-team was created as a forum for both statisticians (industry & academia) and pharmacokinetics as well as regulators to help bridge the gap in the estimands framework with regards to other study types including early phase and clinical pharmacology where the purpose is not confirmatory efficacy. We presented a poster (Does the Estimand Framework Add Value to Clinical Pharmacology Trials?) at the PSI conference 2022. A manuscript is under preparation with focus on bioequivalence/ bioavailability studies and is planned to be published in a clinical pharmacology journal in 2023. The implementation of estimands in early phase studies (including dose finding and CRMs) are also being discussed within this workstream. We aim to share some of our work at the PSI conference 2023.

Communications

In 2022 the homepage of the group was fully revised and summarizes all work of the EIWG.
Posters of the working group were presented at the PSI conference 2022 in Gothenburg and the 7th EFSPI Regulatory Statistics Workshop in Basel.

Estimands in non-inferiority trials

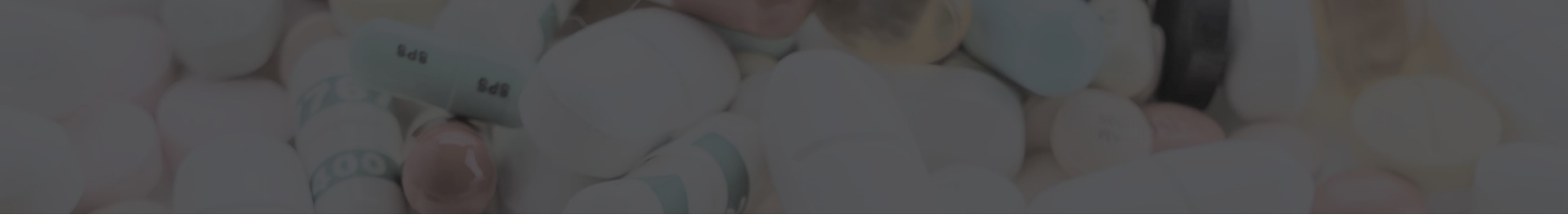
The ICH E9(R1) includes limited guidance in relation to non-inferiority (NI) trials. Current regulatory guidelines on NI trials predate the release of the addendum and the per protocol analysis set plays an important part in the EMA NI guidelines. In contrast, ICH E9(R1) questions the role of the per protocol set and this has led to confusion in regards to the applicability of the EMA Points to consider on switching between superiority and non-inferiority.
The sub-team is discussing which estimands can be considered relevant in a NI setting and how they fit into existing guidelines. The sub-team members are sharing recent regulatory feedback on NI trials, and we are discussing questions such as

- What is the underlying clinical question to be answered in a NI trial?
- Are two estimands with different strategies for intercurrent events required to reflect the spirit in the EMA Points to consider on switching between superiority and non-inferiority?
- Can protocol violations be handled as intercurrent events? Is there any remaining role for a per protocol analysis set?
- Can different estimands be used to show NI and superiority in the same trial (hierarchical set-up)?
- How does the estimand framework impact the choice of the NI margin?

The sub-team is planning to prepare a manuscript on these topics.

EIWG Publications 2022

- A. Morga, NR. Latimer, M. Scott, N. Hawkins, M. Schlichting, J. Wang. Is Intention to Treat Still the Gold Standard or Should Health Technology Assessment Agencies Embrace a Broader Estimands Framework?: Insights and Perspectives From NICE and IQWiG on the ICH E9(R1) Addendum. Value Health. 2022 Sep 20:S1098-3015(22)02148-9. https://doi.org/10.1016/j.jval.2022.08.008
- H. Lynggaard, J. Bell, C. Lösch, A. Besseghir, K. Rantell, V. Schoder, V. Lanius. Principles and Recommendations for Incorporating Estimands into Clinical Study Protocol Templates. Trials (2022) https://doi.org/10.1186/s13063-022-06515-2
- C. Fletcher, N. Hefting, M. Wright, J. Bell, J. Anzures-Cabrera, D Wright, H. Lynggaard, A. Schueler. Marking 2-years of new thinking in clinical trials - the estimand journey. Ther Innov Regul Sci 56, 637–650 (2022). https://doi.org/10.1007/s43441-022-00402-3
- D. Wright, H. Lynggaard , S. Englert, V. Lanius, O. Keene. Why Estimands are Needed to Define Treatment Effects in Clinical Trials. Submitted



ESIG News

HTA ESIG: EUnetHTA21 guideline reviews may be over for now, but EU HTA work continues

What will EU HTA mean for statisticians and how can statisticians influence EU HTA?

Those questions have kept EFSPI/PSI HTA SIG members very busy during 2022. In addition to providing review comments to the many EUnetHTA21 methodological guidelines, a key focus in the HTA SIG has been to build awareness of EU HTA among statisticians. We hosted an informal lunch discussion session at the PSI 2022 conference in Gothenburg in June; we were present at the 7th EFSPI Regulatory Statistics Workshop in Basel with poster presentations; and in November, we hosted a webinar on statistical dimensions of EU HTA that drew +250 attendees. The ESIG's engagements not only spawned a lot of really interesting discussions and perspectives from both statisticians and decision makers, they also grew the HTA ESIG by quite a few members.

With EU HTA only 2 years away, the ESIG's engagement initiatives are far from over. In 2023, we are planning to do more webinars to dive into the methodological aspects of EU HTA - how do we unite estimands and PICOs, for example? We are also planning whitepapers to reflect on the statistical content of the EUnetHTA21 methodological guidelines. And, last but not least, we are aiming for a stronger-than-ever HTA statistical presence at the PSI 2023 conference in London.

We can always use more members to either help drive existing ideas, or to simply bring more good ideas and perspectives to the table. The European Special Interest Groups (ESIGs) jointly sponsored by EFSPI and PSI provide a unique platform for knowledge sharing and scientific exchange going far beyond statistical aspects only and thus foster an incredible collective learning experience. With something as important as EU HTA, we must use that great platform as best we can!

Regulatory ESIG

Draft FDA Guideline on Statistical Approaches to Establishing Bioequivalence

The FDA has recently published for public consultation the guidance on Statistical Approaches to Establishing Bioequivalence, available here. The Regulatory ESIG, jointly sponsored by EFSPI and PSI is collating comments for that, so please send your comments to Jurgen Hummel and Fredrik Öhrn. The FDA have not provided a particular template for the comments, so please provide them using the template provided by ICH, asap but no later than 18 January 2023.

LOCAL ASSOCIATION OF THE MONTH

PSDM
Pharmaceutische Statistiek en Data Management

The PSDM (Pharmaceutical Statistics and Data Management) was founded in 1993 as a working group of the Biometrical Section (BMS) of the Dutch Society of Statistics (VVS). In the early nineties the need was acknowledged to create a national network for professionals working in pharmaceutical statistics and data management. Until that time, people primarily had to travel abroad to gain experience, exchange information or discuss scientific specialist topics of their work. Later on, Clinical Programmers were represented in the board of the PSDM too.

The aim of the PSDM is to facilitate professional conduct and development of its members and to provide a platform for the exchange of expertise and ideas by organizing scientific meetings, workshops, and courses. From the start onwards, the PSDM became an active member of EFSPI. For instance, four times the PSDM delivered the president of EFSPI.

We are a relatively small working group, but before the pandemic slowed us down, we were able to organize great in person meetings on various topics like CDISC (tailored towards data management and programming), biostatistical challenges in R&D and a joint EFSPI meeting on Recent Advances in Clinical Trials. Also, trainings were provided such as a well-received 2-day course on sample size. Although we had limited activities during the pandemic, we are back now and had a nice event on Programming and Statistics in Medical Device Investigation at the beginning of November 2022. In addition, we are in the middle of the planning of a joint 1-day event with EFSPI on data visualization in 2023 and will organize a 1-day course on machine learning for statisticians. More information about the PSDM can be found on our website https://psdm.nl.

Egbert Biesheuvel, chair of the PSDM and Dutch representative in the EFSPI Council

OTHER COUNTRY NEWS

PSI (UK)

PSI Strategy Day

On November 10th the PSI Board met with Committee members and representatives from different parts of the industry and academia for the annual PSI Strategy Day. Topics included the digital strategy, ability of PSI's current offering to meet the needs of our members, what the next generation of PSI will look like and how PSI should evolve to meet all our members' needs. As the world is emerging from the pandemic, it is time for PSI to assess what it offers and provide value to a new generation of members. The discussions were driven by PSI's purpose statement:

"We are a community dedicated to leading and promoting the use of statistics within the healthcare industry for the benefit of patients"

Opportunities were identified in many aeras, and the feedback has given the PSI Board much to work on and prioritize for 2023! A key theme uniting the discussions was the importance of our Digital Strategy to grow our community, drive collaboration and optimize workflows. This will be a key focus for next year.

The Effective Statistician Podcast

→ *Listen here!*

Listen to my podcast and share it with your friends and colleagues who might learn from it.

Ciao and be an effective statistician!

Alexander Schacht

THE PSI 2023 CONFERENCE REGISTRATION PORTAL IS NOW OPEN!

Please click here to register.

The PSI 2023 Conference will be held face-to-face in Hammersmith, London on the 11-14 June 2023. The deadline for abstracts for oral presentations/sessions was 18 November 2022. The deadline for poster abstracts is 25 February 2023. All abstracts should be submitted to PSI2023@wearemci.com.

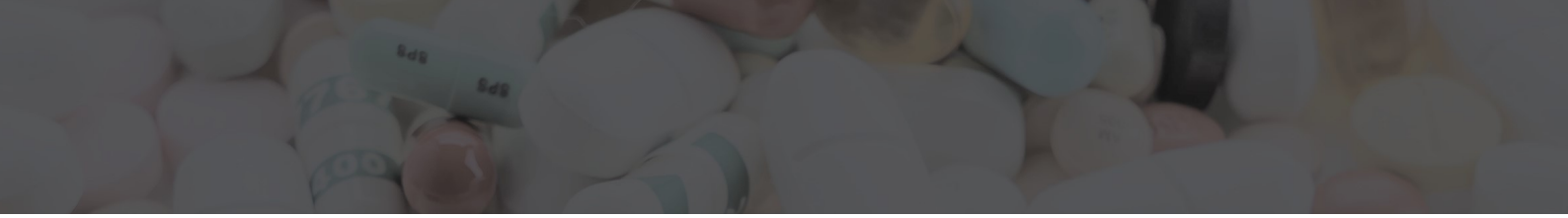
APF (Germany)

As every year, the German APF run their 2022 workshop meeting during the Thanksgiving week. This year, Cytel hosted both APF events, the APF Statistical Leaders workshop on Thursday, Nov 24, and the general APF workshop on the next day. Both workshops were offered as in person meetings in Berlin, which was much appreciated after two years of virtual meetings only. Overall, both events were a big success, with about 30 statistical leaders attending on Thursday and about 90 statisticians showing up on Friday.

For the APF Statistical Leaders workshop, we discussed unblinded safety analysis of ongoing trials for FDA-required causality assessment, on implementation of estimands, and on the across-industry collaboration for open-source R packages.

First, Susanne Schaefer (ICON) shared her experience with implementation of ICH-E9/R1. Although the estimands concept is highly welcomed, it became clear that its implementation poses several challenges for most organizations, incl. a new level of technical complexity for pre-planned analysis. This seems true even for disease areas with established endpoints and a very low degree of expected treatment discontinuation. In particular, specifying the estimand elements and its implementation in the protocol and SAP for all endpoints is quite lengthy with complex technical language. In addition, the move towards MI-based methods to closely reflect ICE-handling, actually only leads to difficult to communicate analysis results, with actually very minor differences in results compared to traditionally used, much simpler analysis methods. With this, it sometimes becomes even more difficult to involve the medical project leads in the planning phase and to communicate the results. In our discussion, we shared various practical approaches, some of which have recently led to publications: Fletcher et al. 2022 and Lynggaard et al. 2022.

On the topic of safety causality assessment to implement FDA's Final Rule, Hans-Juergen Lomp presented the Boehringer Ingelheim set-up and experience with "the trigger approach", where SAE unblinding only occurs if the observed blinded SAE number for anticipated events is above a predefined trigger threshold. In contrast, René Kubiak presented the Sanofi approach (work-in-progress), whereby the causality assessment is based on unblinding of safety data at regular intervals. Both approaches share some core features, such as the setup of a dedicated independent safety analysis team and the pre-specification of detailed statistical rules to support robust causality conclusions. Most importantly, there are great additional benefits of a



dedicated safety analysis team beyond causality assessment for anticipated SAEs, such as supporting adaptive trial designs, DMC handling and an early implementation of project safety analyses. The presentations were followed by lively discussions and experience sharing. Because of its importance, this topic will be again on the agenda at the next Statistical Leaders meeting in April 2023.

Finally, regarding **open-source software collaboration**, APF Statistical Leaders have been successfully promoting respective initiatives since several years: e.g. APF's Service Level Agreement as a support model has been a major enabling factor for the rpact freeware. More recently, in March 2022, APF has run an international workshop on collaboration for open-source R-solutions, specifically dedicated to Statistics and Programming Managers from big pharma, CROs and academia, for more information check out the EFSPI March 2022 Newsletter. At our Berlin workshop, we reflected on the amazing progress since our last meeting. Daniel Sabanes, who co-chairs the ASA Software Engineering WG, presented the strategic focus of Roche towards open-source solutions and shared experience of successful collaboration on R-based GCP solutions, which is coordinated via pharmaverse. Daniel's presentation covered available solutions for building block R-packages, for validation and qualification of large package numbers and for organizational training strategies. During the discussion, we brainstormed how to address the organizational transition from a proprietary SAS-based to an open-source based mixed environment for small and mid-size organizations. Again, due to the strategic importance, this will be a standing topic for future APF Statistical Leaders.

Following the APF Statistical Leaders workshop, the **2022 APF General Workshop** took place. The two focus topics were Planning of Safety Analysis and synthetic control arms to augment RCTs. For **Aggregate Safety Assessment & Analysis**, Juergen Kuebler organized four presentations, covering aggregated Safety Planning Assessment (Juergen Kuebler), Benefit-Risk Assessment Planning (Martin Gebel), upcoming requirements for Safety Endpoints & Analysis for HTA in Europe (Katrin Kupas) and Safety Estimands (Anja Loos). The session closed with a lively panel discussion among presenters, together with Bill Wang (Merck US) and Armin Koch (IfB Hannover). For **synthetic control arms to augment RCTs**, Armin Schueler set the stage with a comprehensive, but entertaining Tour d'Horizon on the subject, followed by two interesting presentations about actual case studies by Ulrich Bayer (Roche) and Marco Ghiani (Cytel). Those case studies led to an engaged discussion about the current and potential future role of synthetic controls for drug approval and reimbursement.

Hans-Jürgen Lomp for APF

JOB OPPORTUNITIES

Nowadays, job opportunities for statisticians and data scientists are excellent!

For information on how to submit recruitment adverts, please visit the Job postings on our EFSPI website.

Are you seeking to hire a statistician and wish to post a job advert? EFSPI is offering one free advert for every 3 adverts posted on the website!

To add your email address to the EFSPI mailing list, click on "Sign up to our newsletter" on our landing page. To view all newsletters please see the "News" area on the EFSPI website.

If not done yet, please follow EFSPI LinkedIn, check out the content and help us to spread the word by reacting to our posts, commenting or sharing!

AND FINALLY...

We value your feedback!
Therefore, please let us know what you think and contact either Justine Rochon or Randi Grøn.

Happy New Year 2023!