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

EFSPI Newsletter February 2020

In this newsletter:

Women in Data

Women in Data was set up 5 years ago, initially with a focus in the UK, but which has since broadened to Europe and beyond, to recognise women who have been influential in professions related to data across all industry sectors. Women in Data aims to promote the value of diversity and inclusion of women in these professions, and to create a forum for where women working in data related fields could share their experiences, network and offer professional development opportunities. Chrissie Fletcher (VP Development Biostatistics, GSK) was one of the 2019 Twenty in Data & Technology awardees, and the first award to be recognised in the Pharmaceutical Industry. Click here to learn more about Women in Data.

Recently Women in Data have launched their Twenty Women in Data & Technology 2020 campaign, click here to watch a video and click here for more details. Given the significant talent of women in the Pharmaceutical Industry it would be fantastic to have more nominations from the EU Statistics Community. Click here to submit a nomination for the ***Twenty Women in Data & Technology 2020*** of inspirational women from your company who are known for their outstanding talent, achievement, innovation and leadership. The closing date is the 8th May 2020.

back to top

Regulatory

The regulatory committee provided comments on the FDA's draft guidance "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products". Thanks to those who provided comments, and to Tony Sabin for collating the comments received.

Annual PSI/EFSPI Regulatory Committee Meetings with MHRA statisticians

I have been a member of the PSI/EFSPI regulatory committee for 13 years now, although it was only a PSI committee when I joined. We have met annually with the MHRA statisticians for an informal exchange during all these years, which is something I've really treasured. Initially we met with Rob Hemmings only, and after a while he brought one of his colleagues with him before gradually including his entire team in the meetings (which had grown itself over time). Sadly, Rob is no longer at the MHRA, but that does not make our exchanges any less interesting. Our latest meeting was held in November 2019. As usual the meeting started with a discussion on topics proposed by MHRA which this year included quality of products, dose escalation methods, real world data, historical controls, extrapolation to paediatric populations, virtual trials, review of protocols for device (non-drug) studies and statisticians in ethics committees. We then went on to discuss the topics we had proposed, which were subgroups, estimands and Quality Tolerance Limits.

MHRA Discussion Topics:

Quality of products (quality attributes): As mentioned at last year's meeting, the team have continued to have a greater involvement in the review of quality assessments (dissolution profiles etc). The use of Mahalanobis distance and the mis-interpretation of a non-significant test as indicating no difference has been observed in some reviews. In particular, the T2EQ method was mentioned and it would be preferable to use bootstrap f2, as noted in the EMA FAQ on this topic. There appears to be a wide variation of methods employed and it is important to ensure that statisticians are involved in the analyses of these quality assessments. There are often separate statistics groups within companies which focus on the product quality and we will follow-up to share this feedback across PSI/EFSPI members.

Dose escalation methods (FIH studies): Model-based approaches are recommended, but it can be difficult for a non-statistical assessor to understand the decision algorithm. The use of separate simulation reports which may be included in a protocol appendix is helpful. However, there is the potential when using a continuous reassessment method (CRM) to permit overdosing within its dose-selection algorithm, and this is of particular concern when reviewing the proposed method. Simulations should therefore investigate how frequently over-dosing will occur under various scenarios. The inclusion of simple summaries (which can be easily interpreted by non-statisticians) is recommended in the simulation report. Comparisons of the CRM approach with the traditional 3+3 method may also be beneficial.

Real World Data: Companies have been using the Innovation Office to discuss Real World designs and the MHRA statisticians are also involved in the joint HMA/EMA Big Data Task Force. The key question which must be clearly considered in the design is exactly what we are trying to estimate and what data is needed in order to do this, from there we can consider whether all the data needed would be available through the use of Real-World data sources. Pragmatic randomised trials in the real-world setting (e.g. GP surgeries) may be an option to assess efficacy of drugs with well-known safety profiles.

Historical Controls: The MHRA view on historical controls has not really changed and they should only be used if there is really no other option, the key difficulty is trying to convince that the populations are comparable. It should be noted however, that in rare diseases where the natural history of the disease is well known, the primary endpoint is an objective measure and the treatment effect is so large as to overcome any doubts on the possible biases introduced by selecting certain historical controls, this type of design has been accepted for licensing.

Drug developers are asking if historical controls can be used if they are able to ascertain very good controls, matches, control of type I error etc then can they [historical controls] be used, and would this be acceptable from a regulatory perspective. The MHRA consideration is what if the assumptions don't hold, and in particular, if there were discrepancy between concurrent and historical controls then this would be problematic. Historical controls are a possibility in this context but discussions are still ongoing and could expand as more opportunities arise with more data and sponsors are encouraged to discuss their proposals with the MHRA.

Extrapolation to paediatric population: The challenge is to balance the strength of the model assumptions with the actual data collected. If a drug is successful then how could this be extrapolated to paediatrics, and, how would the safety aspects be considered without data collected (for paediatric patients). There is a potential to obtain some of this from Real-World data, but inspectors may have concerns and the data may be questionable.

Virtual Trials: The topic of virtual trials was also covered and the greater suitability of this type of trial in the context of objective endpoints. The MHRA view is that in principle virtual trial would be ok when well designed, but there are concerns around safety and monitoring as patients do not have the same access to physicians. There is also likely to be higher variability on background care compared to studies conducted in centres.

Review of Protocols for Device (non-drug) Studies: The MHRA statisticians have continued to be more involved in the review of protocols for devices which can have limited statistical planning and only brief statistical sections. This highlights, again, that statisticians' involvement in device trials is often lacking.

Statisticians in ethics committees: It has come to the attention of the MHRA that only a minority of ethics committees in England have statisticians (<40%). MHRA is trying to raise awareness of this issue with HRA (the Health Research Authority) and trying to seek a solution to the problem. Can member Companies help support the appointment of statisticians to the ethics committees? We felt that there may be a conflict of interest for industry statisticians to be directly involved as members of an ethics committee, but that this question could be explored and followed-up within our companies.

PSI/EFSPI Discussion Topics:

Subgroups

Question: Can you tell us your impressions of what the major changes between the draft and final versions of the EMA subgroup analysis guideline are?
Discussion: The changes between the draft and final guideline were mainly to restructure the document. Although there may appear to be some new concepts introduced; use of a broad population study and a possible focus on subgroups which may have an impact on the indication, these were not intentional.

Estimands
Question: In anticipation of the ICH E9 R1, to be released soon, it would be good to hear about the experience as well as expectations from a regulatory point of view regarding estimands.

- What do you feel is the value of the various strategies for handling intercurrent events?
- Would there be different perspectives for efficacy versus safety in handling intercurrent events and subsequent estimand descriptions?
- What are your impressions of what have been seen thus far in protocols submitted for regulatory review? To what level has estimands been described in submitted protocols?
- What are the expectations going forward, as a final guideline becomes available?
- Assume the estimand specifies the indication as "follicular lymphoma". The actual trial recruits 1000 patients, 980 in follicular lymphoma and 20 in DLBCL (this is inspired by a real example!). Today, we would according to ITT analyse all 1000 patients as randomized. However, this "ITT estimator" does not estimate the estimand based on the "follicular lymphoma" population attribute. So, in a post-addendum world, would we remove the 20 DLBCL patients, in line with the addendum?

Discussion: The MHRA statisticians are seeing the incorporation of estimands in the protocols submitted for review. They emphasized that they are currently learning as much as industry how to apply the framework put forth in the ICH E9 addendum.
It is obviously not possible to give blanket recommendations on the appropriate use of the various intercurrent event strategies. However, some general comments were shared on the different approaches:

- The treatment policy is quite useful depending on the circumstances, but an example of where it could be misleading is one where many placebo patients take rescue therapy.
- The composite strategy can be particularly useful for dichotomous endpoints but should not lead to an artificial dichotomisation of events. Terminal events were also highlighted as an example of when this strategy was likely to be useful.
- The hypothetical estimand is mentioned in some disease guidelines and could be useful in cases where rescue medication is used. However, it would not be applicable in cases where its use means patients are assumed to have benefitted from treatment but in reality, they did not.
- While-on-treatment strategy was rarely used but could be useful in some specific cases such as palliative care in cancer, but would not be appropriate if the inter-current event that led to stopping the treatment was related to treatment.
- Principle stratification – struggling to figure out how to apply in practice. It seems to have relevance in the analysis of crossover trials, where it could justify the approach of including only patients who complete both periods.

On the question of whether the estimand approach could be used for safety endpoints, it clearly could be, as the idea is just to encourage a clear definition of how missing data will be handled. The need for this might depend on the objectives of the trial, and if safety endpoints will be formally analysed. The estimand approach may therefore be more necessary in situations where safety is considered as a co-primary endpoint with efficacy. The choice of estimand might be different for the same endpoint depending on whether it is being considered for efficacy or safety. For example, a

cardiac endpoint could be handled differently depending on whether it is an efficacy trial (where the treatment is expected to prevent events) or a safety trial (where it may cause them).

It is also possible that there may be country specific requirements for estimands and we've previously seen this requirement addressed within the Statistical Analysis Plans in situations where, for example, a single primary endpoint could not be agreed across regions, and this is not a new issue specific to estimands. It is important to ensure that data are collected for all endpoints/estimands of interest and to seek scientific advice in relation to the construction of estimands in this regard.

There do appear to be more protocols which follow patients after the discontinuation of therapy, and this is a positive outcome from the introduction of the estimand concept. However, despite the implementation of estimands within protocols, the reviewers have seen examples of mismatches between the estimand and the actual analysis method.
With regards to the interpretation of an Intention to Treat population, if patients are entered into a clinical trial in error and this is not expected to occur in clinical practice then it may be appropriate to exclude these patients from the analysis. However, this is not a new view related to the introduction of the estimands concept and this would have applied previously.

The introduction of estimands into protocols is still evolving and will continue to do so with the implementation of the ICH E9 addendum. The MHRA statisticians are working with their clinical assessors to assist with transition to the implementation of estimands. MHRA is expecting the use of the principles of the framework but not necessarily the actual language from the addendum. However, the CHMP have been asking 'what is your estimand?' so it may be that this evolves further over time. The importance is to improve the up-front thinking in planning clinical trials through the introduction of the framework; this is likely to require more involvement from statisticians at the protocol development stage.

Quality Tolerance Limits (QTLs)
Discussion: As mentioned at last year's meeting, to-date there has not been much involvement by the MHRA statisticians in the implementation of this new concept, as it is not within their remit. The visibility of the topic may increase once they begin to see Clinical Study Reports for studies employing QTLs. The PSI/EFSPI committee confirmed that this is a very active area, with a lot of statistical input cross industry. There is broad agreement that in principle it is sensible to take corrective action when for example the proportion of patients included in the study in error is higher than expected (as this would indicate that the protocol was not clear enough on some of the criteria), but there is potential for such actions to lead to trial modifications which may have bias implications.

Jürgen Hummel (PPD), on behalf of the PSI/EFSPI Regulatory Committee

back to top

Scientific

The Scientific Committee is planning for a number of events in 2020. Although none of them have a confirmed date, these are our intended meeting in preparation for 2020:

- A one-day meeting on Soft **skills of a statistician**, with a planned date in the end of the first quarter, beginning of the second quarter. Rather than a course, the focus will be more on an overview of skills needed to be impactful, and the link to communication and the core of our profession.

- A joint BBS/EFSPI/PSI seminar will be organized together with the European SIG "**Estimands in Oncology**"' on this topic in Basel, 29th June 2020.

- A joint EFSPI/BBS meeting on **Health technology Assessment**, looking back at '10 years of HTA' and looking forward. This 1-day meeting with take place in Basel, 30th June 2020.

- A meeting on **Vaccines**, jointly organized with the Belgian Association (SBS/BVS) and the SIG on Vaccines. The aim is to have a combination of a course and a scientific meeting, which will take place in October near Brussels.

- A meeting together with the SIG on **Small Populations** in the second half of 2020

As soon as we have more concrete information, we will share with you via the Newsletter and our website.

Defining Multimorbidity in Clinical Trials

Multimorbidity, the presence of two or more health conditions rather than a single standalone health condition, is very common and a major issue in healthcare globally. Patients with multimorbidity are less likely to receive guideline-recommended treatments and many clinical guidelines are equivocal on the applicability of trial findings to multimorbid patients. To help to address this uncertainty, the International Research Community on Multimorbidity (IRCMo - http://crmcspl-blog.recherche.usherbrooke.ca/) are seeking to develop standards for measuring and reporting on multimorbidity in clinical trials of drug interventions. They are looking for interested partners in either academic or industrial settings. If you might be interested in getting involved, please email definingmultimorbidity@glasgow.ac.uk

back to top

ESIG News

Toxicology

The Toxicology ESIG are pleased to announce the following events:

Webinars:
March 31st: Label-free Classification of Ciliated Cells using Deep Learning – Ketil Tvermosegaard (GSK)
June 23rd: Reproducibility from Discovery to Clinical Research – Bruno Boulanger (Pharmalex)

Workshop:
March 16-17th: Annual Workshop including a half day course on Bayesian Analysis of Pre-Clinical

Studies. Heathrow, UK.

For more information on any of these events please contact Gareth Thomas at gareth.thomas@covance.com

Would you be interested in working with the ToxSIG Committee?

As a group of Statisticians working within Toxicology, but covering wider pre-clinical/non-clinical areas, the ToxSIG committee hold regular TCs, organise up to 4 free webinars per year and run an annual 2-day workshop. Being a committee member does not take up significant time but has presented a number of advantages to both past and present committee members. The committee are currently looking for more companies to be represented on the committee. We currently have representatives from Boehringer Ingelheim, Covance, Janssen (JnJ) and GlaxoSmithKline. If you work within a related pre-clinical area and would like to be involved in this wider support network, please get in touch.

Members of the Toxicology Special Interest Group committee have found this to benefit them in the following ways:

- Helps to forge partnerships with statisticians across the industry with a common goal
- Engage with some of the experts in this field
- Opportunities to be involved in writing or contributing to published papers
- Identifies who to contact when asked about an out-sourced study
- Learning on a regular basis about the work being performed in other companies
- Improving personal influencing, communication and organisational skills
- Influencing the choice of webinar topics to broaden own learning
- Promoting and increasing exposure for own Company and the innovative work performed in related areas

For more information and to express an interest in joining the committee, please email gareth.thomas@covance.com.

New Visualisation special interest group (VIS SIG)

Effective visualisation of data should belong to the core skills of statisticians as it represents an essential tool in exploring data as well as explaining data.

The visualisation special interest group (VIS SIG) has formed itself to:

- Lead a cultural change to look beyond tables alone
- Train statisticians and other quantitative scientists to learn about effective visualisations and data storytelling
- Develop recommendations and best practices for the healthcare field leveraging learnings from other areas
- Establish a gallery of case studies for the rich field of data used in healthcare including traditional and new data sets (e.g. brain scans, wearable data)
- Improving the understanding of the richness of data and the uncertainty of estimates.

The current core team Mark Baillie (Novartis), Zak Skrivanek (Lilly), Rachel Phillips (Imperial), Bodo Kirsch (Bayer), Lorenz Uhlmann (Novartis), Daniel Saure (Lilly), and Alexander Schacht (UCB) work on several events both online as well as in-person to achieve these goals.

Learn more about the VIS SIG and register your interest in upcoming events here.

back to top

Country News

AFP (Germany)

On March 16th, 2020 APF is co-organizing a workshop on 'Analysis of adverse events in the context of estimands' in Heidelberg. The program can be found here: https://www.klinikum.uni-heidelberg.de/medizinische-biometrie/veranstaltungen/workshop-16-maerz-2020.

The next German statistical leaders meeting will take place on the 27th March 2020 at BMS in Munich.

IBIG (Italy)

On the 6th – 8th May, Turin. IBIG with the EFSPI patronage: Training Course on Early Phase Clinical Trials held by Prof. Thomas Jaki and Dr. Pavel Mozgunov (Lancaster University). Details at http://www.biostatistici.it/training-e-corsi/ . For info email to marco.x.costantini@gsk.com or giulia.x.zigon@gsk.com.

DSBS (Denmark)

On 3-4 February 2020 the DSBS hosted a course on Causal Inference with senior researcher Arvid Sjölander from Department of Medical Epidemiology and Biostatistics, Karolinska Institutet. The course was well attended (34 participants), with all available seats used. The course described the fundamentals of Causal Inference introducing potential outcomes, counterfactuals and DAGs and continued with marginal causal effects and instrumental variables.

On 9 March Professor Mark van der Laan from University of California, Berkeley, will give a joint DSBS/DSTS biostatistics seminar titled: "Targeted Learning, Super Learning, and the Highly Adaptive Lasso". More information can be found on the DSBS website https://dsbs.dk/.

PSI (UK)

2020 PSI Conference

The conference theme for 2020 is "Shaping the Future of Statistics" and will take place in Barcelona on 7th-10th June 2020. To register to attend the 2020 PSI Conference in Barcelona and book your pre-conference course place, please click here. To find out more information about the Conference - such as the venue, pre-conference course information, or sponsorship, please visit the PSI website.

PSI Training Course: R for SAS Users

Date: Tuesday 24 & Wednesday 25 March 2020
Time: 09:30 - 17:00 (Tuesday) & 09:00 - 16:45 (Wednesday)
Location: Crowne Plaza, London Heathrow

This course is aimed at statisticians and programmers who may be experienced in SAS, but have had no, or little experience in R. R is becoming a popular statistical package in the pharmaceutical industry. R offers many benefits over traditional statistical packages, with enhanced graphical capabilities and extensive simulation abilities. This course will be a hands-on deep dive into R, so attendees should bring a laptop with the latest versions of R and R studio installed. Click here to register.

PSI Scientific One Day Meeting: Missing Data in Clinical Trials - Past, Present & Future

Date and location: 28 April, 2020, GSK House, Brentford TW8 9GS, UK

Presenters: David Brown (MHRA), David Wright (AstraZeneca), Simon Day (CTCT Ltd), Michael O'Kelly (IQVIA), Daniel Bratton (GSK), James Roger (Livedata), and Mouna Akacha (Novartis)

Incomplete datasets due to missing data is an issue that has been, and will be, around for a long time. At this meeting knowledgeable speakers from health authorities, academia and pharma will present the evolution of missing data approaches, looking at how they have been handled in the past, the current established missing data approaches and the impact of the new ICH E9 R1 addendum on the handling of missing data, focusing in particular on the treatment policy estimand.

Full details of the meeting including speaker biographies, abstracts, and registration information are available at:

https://www.psiweb.org/events/event-item/2020/04/28/default-calendar/psi-scientific-one-day-meeting-missing-data-in-clinical-trials---past-present-future

Visit the Video-on-Demand Platform here!

PSI ToxSIG Webinar: Big Data, Data Science, AI & other Buzzwords

Richard Pugh

The last 15 years has seen a massive shift in the role of data and analytics, driven by the increased hype around big data, data science, machine learning and AI. This presents both challenges and opportunities for analytic teams. This webinar will strip back the hype to look at what these buzzwords really mean, and talk about the impact this is having on the role, remit and operating model of analytic teams in the life sciences industry.

Click here to watch

THE EFFECTIVE STATISTICIAN PODCAST
IN ASSOCIATION WITH

Impact of AI in clinical development

Interview with Karim Malki

With so many recent advances in AI, it is important for statisticians to both keep up to date with the most recent methods and getting involved in guiding their application to the most pressing statistical challenges.

In today's episode, Karim and I cover cutting edge examples of how data science and statistical sciences are intersecting. Learn from this episode why different

approaches matter when looking at clinical development data.

How and why to increase your external profile!

Interview with Liz Cole
Do you know what your external profile is? Do you know how to improve it?
In today's episode, Liz Cole and I will dive deep into a topic called content marketing. It's kind of meta, since this podcast itself originates on these ideas. Does this sound frightening or disturbing? It shouldn't. Listen to our conversation and understand.

RWE demystified

Interview with Imi Dean
There are lots of buzzwords floating around and especially with the FDA having a bigger focus on RWE it's top of mind for many stakeholders. Many teams in the different pharma organizations concentrate on this type of evidence.
In this podcast episode, we will explain some of these topics, bust some myths and help you understand how this data fits into the bigger picture.

Listen to these podcast episodes now and share it with others who might learn from it. Ciao and be an effective statistician!
Alexander Schacht

back to top

Volunteers needed

EFSPI are seeking volunteers to join an EFSPI Communications committee. If you have expertise in using a variety of communication channels and you have ideas and suggestions for how EFSPI could improve the website and its use of social media, please contact Chrissie Fletcher (chrissie.a.fletcher@gsk.com).

back to top

Job Opportunities

Job opportunities exist for Statisticians in different levels of seniority in clinical development, click here to view the job advert. For information on how to submit recruitment adverts, please visit the EFSPI website: Job postings. If you are currently seeking to hire a statistician and wish to post a job advert, EFSPI are offering one free advert for every 3 adverts posted on the website.

back to top

Follow us on Twitter and LinkedIn

Get the latest news and updates about EFSPI by following us on Twitter at @EFSPItweet. Also, when you use Twitter to spread the word about EFSPI, be sure to use the hashtag "#EFSPI". You also can follow developments in EFSPI via LinkedIn.

back to top

And finally.....

To add your e-mail address to the EFSPI mailing list, click on "Sign up to our newsletter" on the homepage of the EFSPI website.

To view previous newsletters please see the EFSPI website in the "News" area.

back to top

Chrissie Fletcher
EFSPI Communications Officer