Minutes from Virtual Meeting between EMA Statisticians, EFSPI Stats Methods Leaders Group

19 May 2026

Attendees:

European Medicines Regulatory Network (EMRN): Elina Asikanius, Benjamin Hofner

EFSPI: Jürgen Hummel (Cytel, chair), Mouna Akacha (Novartis), Nicky Best (GSK), Rachid El Galta (Sandoz), Klaus Kähler Holst (Novo Nordisk), Philip Hougaard (Lundbeck), Mike Krams (Berry Consultants), Tobias Mielke (J&J), Alex Ocampo (Roche), Kaspar Rufibach (Merck Healthcare KGaA), Kert Viele (Berry Consultants), David Wright (AstraZeneca)

Topic	***Questions* and Notes**
Open question to regulators: What gaps do you observe that we could help improve?	**EMRN:** • EMRN statisticians work as assessors on a case-by-case basis, and everything is done in writing, making it more difficult to discuss general issues. • Clear written communication is essential from both sides; a high-level summary of the innovation and its rationale, supported by a detailed technical report, may help. • It is helpful for methods groups to understand regulators' day-to-day assessment environment and constraints • The quality of submissions is often suboptimal, exemplified by making an MMRM for a single post-baseline measurement, or confusing non-significance with the absence of an effect. • Many submissions include new methodology. EMRN statisticians need to clearly understand the "why" behind a proposed method. This should be clear and well explained. Regulators need "good literature and good rationale" for methodological proposals. • Proposals often disregard fundamental concepts such as unbiased estimators, Type I error control, and building confidence intervals. Such aspects should be covered in the proposal as applicable. • Sufficient information should be provided so that assessors can explain and defend innovative proposals internally to internal stakeholders • The EMRN has pathways to seek for internal alignment through the Methods Working Party for new/precedence setting cases • EMA qualification opinions cover a specific context of use and not the principle of a new method • Past EMA Workshops (Bayes, External Controls) were particularly organized to hear and learn from industry. **EFSPI:** • Dialogue more helpful, when it is informal.
Bayes	**EMRN:**

	• EMRN statisticians are not specifically for or against Bayesian methods; acceptability depends on the scientific context, purpose, and adequate justification. At present, Bayesian submissions are challenging to navigate through the regulatory process. • There is a clear need for further education and capacity building on Bayesian methods across regulators and industry. While training opportunities by industry or academia are welcomed, a dedicated training from industry to regulators only is not considered possible and sensible. Training opportunities should be open to all stakeholders. • Simply citing published papers is generally insufficient; sponsors need to provide a transparent, well-structured justification tailored to the specific development context and decision problem. • While the idea of a "mock Bayesian submission package" was viewed positively in principle, the EMRN does not have an official route to assess such "exploratory" packages. • Well-prepared meeting and submission packages are essential to enable constructive scientific dialogue and efficient review. • Concerns around control and interpretation of Type I error remain an important consideration in Bayesian applications in a confirmatory setting. • In the context of paediatric extrapolation and ICH E11A, for Bayesian borrowing or trial augmentation approaches, the primary discussion should first focus on the scientific rationale for augmentation and the underlying clinical question; methodological implementation should follow from a clear articulation of purpose. • The discussion should focus on principles and context of use, rather than innovation for its own sake. • Scientific advice interactions were viewed as particularly important for complex Bayesian approaches. **EFSPI:** • It would be helpful to separate discussions on Bayesian methods more broadly from discussions specifically focused on external data borrowing. • Training opportunities were strongly welcomed for both regulators and industry. • There was broad agreement that discussions should be principle-driven, with emphasis on transparency, scientific rationale, and clarity of communication.
Covariate adjustment	**EMRN:** • There are only few submissions with synthetic covariates (super-covariates), combining multiple measurements into a single prognostic index. There are similarly not many using machine learning.

	• Synthetic covariates are problematic as they are not interpretable. There is concern with the underlying scientific rationale/purpose if each company comes with their own synthetic covariate. • Covariates should be split into prognostic and predictive. This should be reflected in the protocol and the corresponding methods. • There is some skepticism regarding whether sample sizes should be reduced at all due to covariates. A sufficient sample size is still needed e.g. for safety, secondary endpoints, and subgroup analyses. • A strong covariate effect might suggest that there are differential effects in subgroups, and these should be examined by other methods, such as considering each subgroup alone. • The distinction between marginal vs. conditional effects and their relevance in a given situation is a key consideration. **EFSPI:** • Federated learning where companies work together on common definitions and publications of synthetic covariates could be one approach forward • EFSPI noted that the requirement for interpretability of prognostic scores used in covariate adjustment deserves further discussion. When the sole purpose of a score is to improve precision, it is unclear why interpretability should be essential. More generally, prognostic scores offer a way to design feasible studies while preserving the original population and endpoint, which may be preferable from a scientific standpoint to other common approaches for reducing sample size, such as narrowing the inclusion criteria or modifying endpoints.
Open question to regulators: How do you see our group within the broader scientific community? Any suggestions?	Not covered in the discussion