Workshop on the use of Bayesian statistics in clinical development

17 June 2025

Summary Report

Contents

Disclaimer

This report summarises the main discussions and insights from the workshop, aiming to support ongoing methodological development and foster the appropriate and consistent use of Bayesian approaches for evidence generation to support regulatory decision-making across the EU. The views and reflections summarised below do not represent the official position of the EMA or any of its committees or working parties. Nor should they be construed as reflecting a consensus amongst participants or formal outcomes of the workshop.

Executive Summary

On 17 June 2025, the European Medicines Agency (EMA) hosted a multi-stakeholder workshop on the use of Bayesian statistics in clinical development. Organised under the Methodology Working Party's (MWP) 2025–2027 workplan and the ACT-EU initiative, the workshop brought together representatives of regulators, industry, academia, patient organisations and health care professionals to explore the opportunities and challenges associated with Bayesian methods in regulatory settings.

Bayesian approaches offer a flexible framework for integrating prior knowledge in a formal and scientifically rigorous way and enable quantification of uncertainty on the quantity of interest as well as on predictions for new data. The workshop focused on their application in areas such as rare diseases, paediatric extrapolation, and adaptive designs.

Key themes related to the use of Bayesian statistics in clinical trials included ensuring appropriate characterisation and understanding of operating characteristics (e.g. type I error) of the design, strategies for robust and transparent prior specification, and the importance of sensitivity analyses. Particular attention was paid to the principles and limitations of borrowing external data, especially in the context of small populations.

The event also served as a platform for gathering stakeholder input to inform the development of future EMA guidance on Bayesian methods. Discussions highlighted the need for clear regulatory expectations, harmonisation with international initiatives (e.g. ICH E20), and continued dialogue between stakeholders.

Objectives and Agenda

The objectives of this workshop were to:

- Discuss the potential benefits and challenges when using Bayesian statistics in clinical development
- Discuss what information might be useful and relevant to include in upcoming guidance documents
- Better understand the trial designs that are being proposed and used, so that future guidance is fit for purpose

The workshop began with a welcome session, setting the stage for the discussions ahead. Following this introduction, the program was organised into five sessions. Each session consisted of two to three presentations, followed by a Q&A segment, allowing participants — including patient representatives, healthcare professionals, academic researchers, regulatory authorities, and industry — to pose questions, exchange views, and further enrich the dialogue.

During the workshop, 14 presentations were delivered and summaries can be found in Appendix 3 of this report. The presentation slides of the 13 speakers who consented to publication are available on the Agency's website at Workshop on the use of Bayesian statistics in clinical development | European Medicines Agency (EMA).

The workshop had the following agenda:

Welcome and opening remarks

- Opening remarks from Peter Arlett (Head of EMA's Data Analytics and Methods Taskforce)
- *ACT EU and the importance of methodological innovation* by Marianne Lunzer (Chair of the Clinical Trials Coordination Group (CTCG) and the ACT EU Steering Group)
- *Bayesian Statistics in Regulation: Panacea or Pandora's Box?* by Kristin Karlsson (MWP vice-chair)

Session 1: Introduction to Bayesian statistics and decision making

Chairs: Frank Pétavy (EMA) and Aysun Cetinyurek Yavuz (MEB-CBG)

Bayesian borrowing in clinical trial test decisions: Frequentist type I error rate and power
Annette Kopp-Schneider (German Cancer Research Center, Heidelberg)

Benefits and challenges of using Bayesian methods to support regulatory decision-making
Nicky Best (EFPIA/EFSPI)

Session 2: Upcoming Guidance – Challenges and Opportunities

Chairs: Martin Posch (Medical University of Vienna) and Juan Jose Abellan (EMA)

EU Concept Paper on the use of Bayesian statistics in clinical development
Peter van den Ven (MEB-CBG)

ICH E20 – an industry perspective
Frank Bretz (EFPIA/EFSPI)

ICH E20 – a regulatory perspective
Frank Pétavy (EMA)

Session 3: Use cases of Bayesian statistics I

Chairs: Tobias Fellinger (AGES) and Florian Lasch (EMA)

Bayesian methods without borrowing in ultrarare diseases
Natalia Muehlemann (EFPIA/EFSPI) and Jan Priel (EFPIA/EFSPI)

Bayesian adaptive design for a practice-changing platform trial in a rare paediatric cancer: The Glo-BNHL Trial
Lucinda Billingham (University of Birmingham)

Bayesian modelling to handle intercurrent events and facilitate interim decision making
Nicky Best (EFPIA/EFSPI) and Prashant Dalvi (EFPIA/EFSPI)

Session 4: Use cases of Bayesian statistics II

Chairs: Peter van de Ven (MEB-CBG) and Juan Jose Abellan (EMA)

Leveraging information for a key secondary endpoint across adjacent populations
Simon Wandel (EFPIA/EFSPI) and Anastasia Lesogor (EFPIA/EFSPI)

Bayesian borrowing for paediatric extrapolation: the DINAMO study
Martin Oliver Sailer (EFPIA/EFSPI) and Igor Tartakovsky (EFPIA/EFSPI)

A Regulator's Perspective on Paediatric Bayesian Methods
James Travis (FDA)

Session 5: Use cases of Bayesian statistics III

Chairs: Kristin Karlsson (MWP Vice-Chair) and Manolis Efthymios (EMA)

Bayesian shrinkage methods for routine estimation of subgroup treatment effects
Björn Bornkamp (EFPIA/EFSPI) and John McMurray (University of Glasgow)

Application of ICH-M15 for Bayesian Modelling - Using a systematic model assessment framework to support design submission and discussion
Tobias Mielke (EFPIA/EFSPI)

Closing remarks

Concluding remarks by Peter Arlett (EMA)

Welcome and setting the scene

Opening messages

- The workshop commenced with Peter Arlett welcoming all participants, both in person (around 50) and online (over 450), highlighting the potential of Bayesian methods as complementary tool to traditional statistical approaches and encouraging participants to actively engage in discussions.
- Marianne Lunzer, Chair of the CTCG and member of the ACT EU Steering Group, then spoke about the role of ACT EU and why methodological innovation is essential for modernising clinical trials in Europe, setting the context for the discussions ahead.
- This was followed by Kristin Karlsson, Vice-Chair of the Methodology Working Party (MWP), who reflected on the opportunities and challenges of using Bayesian approaches in regulatory decision-making, framing the central theme of the workshop.

Summary opening remarks Peter Arlett (EMA's Head of the Data Analytics and Methods Taskforce)

Bayesian statistics are gaining attention as a powerful tool in clinical development, offering opportunities to accelerate the path from innovation to safe and effective medicines. While traditional statistical methods remain central to regulatory decision-making, Bayesian approaches can complement them by enabling more flexible and efficient trial designs, particularly in scenarios where borrowing external information or adaptive designs are beneficial.

EMA, together with its Methodology Working Party, is actively exploring how Bayesian methods can be integrated into regulatory frameworks. This workshop serves as a platform for stakeholders and experts to share perspectives that will inform upcoming guidance, including a reflection paper subject to public consultation.

The day's agenda includes introductory sessions on the regulatory context and references to international guidance such as ICH E20 on adaptive clinical trial designs, followed by case studies demonstrating Bayesian applications in various clinical settings. These discussions aim to shape practical considerations for future guidance in Europe, ensuring robust and scientifically sound use of Bayesian methods in regulatory decision-making.

Summary opening remarks Marianne Lunzer (AGES)

The workshop on Bayesian statistics in clinical development brings together a diverse group of stakeholders: patients, healthcare professionals, regulators, industry, and academia, reflecting a shared commitment to advancing innovation while maintaining scientific integrity and public trust. This event is part of the Accelerating Clinical Trials in the EU (ACT EU) initiative, which aims to transform the European clinical research landscape through collaboration and methodological excellence.

ACT EU fosters an environment for open dialogue to address common challenges and ensure Europe remains competitive globally. Central to this effort is the modernization of clinical trial design and analytics, including adaptive designs, Bayesian approaches, and the integration of real-world data. These innovations enable more flexible, efficient, and patient-centric trials, supporting faster medicine development, reducing resource use, and enhancing ethical standards by minimizing patient exposure to ineffective treatments.

Harmonised and transparent methodological standards are essential to build trust and achieve regulatory convergence. Expert groups such as MWP and CTCG play a key role in guiding best practices. Through collaboration, Europe can remain at the forefront of methodological innovation, accelerating the delivery of safe and effective medicines to patients.

Summary opening presentation by Kristin Karlsson (MWP vice-chair)

The presentation introduced the growing interest in Bayesian methods within medicine development and explained why guidance is needed. These approaches are increasingly referenced in international guidelines such as ICH E11A and ICH E20, as well as in ACT EU documents on complex trials. They offer opportunities for innovation by allowing prior information to be formally incorporated into analyses and enabling more flexible trial designs. At the same time, their use raises questions about interpretation, transparency, and regulatory acceptability, making clear guidance essential.

The presentation emphasized the importance of understanding both the strengths and limitations of Bayesian methods. Key considerations include how to assess uncertainty, ensure robustness, and maintain confidence in regulatory decisions. To this end, a concept paper on the use of Bayesian statistics in clinical development is under preparation. The workshop aimed to foster dialogue on the use of Bayesian methods, if and how they can become a practical tool for regulatory decision-making, including how to best manage new complexities linked to their use.

Session 1

Introduction to Bayesian statistics and decision making

Key messages of Session 1

- Bayesian borrowing can improve efficiency by incorporating external data, but under strict frequentist evaluation it may inflate Type I error.
- Hybrid control arm designs, where a smaller control arm is supplemented with external controls, coupled with adaptive borrowing require transparent assumptions and rigorous calibration to achieve regulatory acceptability.
- Bayesian methods offer advantages such as direct probability statements, evidence synthesis, and prediction of future data in support of interim decisions, making them valuable for complex and rare disease trials.
- Successful implementation depends on early dialogue with regulators, clear justification of priors, and robust frameworks to manage potential prior-data conflict and ensure transparency.

The first session provided a comprehensive introduction to the role of Bayesian statistics in decision-making, contrasting its utility with traditional frequentist frameworks. A primary focus was the mechanism of Bayesian borrowing and its impact on clinical trial design. Prof. Annette Kopp Schneider highlighted the tension between incorporating external data to improve efficiency and the necessity of maintaining strict type I error control required by regulators. The analysis demonstrated that while hybrid control arms and adaptive borrowing are conceptually appealing, they demand rigorous calibration. Under strict frequentist evaluation, borrowing does not inherently increase power and can inflate error rates, suggesting that the true value of these methods lies in their ability to formalize assumptions about data similarity rather than merely bypassing statistical constraints.

Building on the technical challenges, Prof. Nicky Best discussed the broader regulatory landscape and the operational opportunities for Bayesian methods. Despite their established use in early-phase trials and internal decision-making by medicine developers, adoption in confirmatory settings remains cautious. The presentation underscored the advantages of Bayesian frameworks, such as providing direct probability statements, facilitating evidence synthesis, and supporting interim decision-making, which are particularly valuable for rare diseases and high unmet needs. However, the successful implementation of these designs requires early and transparent dialogue with regulators to justify prior assumptions and manage potential prior-data conflicts.

Together, the presentations emphasized that, while Bayesian methods offer a robust alternative to frequentist designs, their application requires a clear understanding of the trade-offs between efficiency, flexibility, and regulatory rigor.

Q&A and discussion

The Q&A session explored the challenges and nuances of comparing Bayesian and frequentist approaches in clinical trial design and interpretation. A key topic was type I error and alternative metrics that could be used in the Bayesian paradigm, including the concept of "average type I error" over a *design prior* and how it might be applied to characterize the risk of a wrong positive conclusion. It was emphasized that Bayesian designs require considerations around plausible ranges of parameter values, unlike frequentist designs which typically control error rates across all possible values of the parameter. The discussion highlighted the importance of using multiple metrics to evaluate and manage risks rather than relying on a single measure.

Another major theme was regulatory acceptance of Bayesian methods. A case was discussed where the FDA accepted a Bayesian-based result while the EMA did not, suggesting differences in trust and interpretation of prior information. The panel stressed the importance of pre-specifying Bayesian 'success' criteria during the design phase and using sensitivity analyses to assess the robustness of results. The conversation also touched on internal resistance within pharma companies due to perceived regulatory reluctance, and the need for more training and capacity building as a key factor in increasing adoption of Bayesian methods.

Finally, the discussion broadened to the foundational issue of agreeing on the data-generating model before choosing an inferential framework. It was argued that good experimental design should focus on understanding variation and assumptions, rather than being strictly Bayesian or frequentist. Simulations were noted as a common tool requiring alignment on these models, reinforcing the need for transparent discussions early in the trial planning process.

Session 2

Upcoming Guidance – Challenges and Opportunities

Key messages of Session 2

- EMA is developing a concept paper outlining the scope of a future reflection paper to clarify when and how Bayesian methods can be appropriately applied in clinical development, aiming to ensure transparency, robustness, and regulatory confidence.
- Potential applications include, but are not limited to, extrapolation, adaptive designs, and shrinkage estimation, but these require prespecified priors, sensitivity analyses, and strategies to manage prior-data conflict.
- ICH E20 provides global principles for adaptive designs, emphasizing rigorous planning, Type I error control, and trial integrity. Bayesian methods within this framework may demand additional justification and documentation.
- Both industry and regulators stress the importance of early engagement and clear communication on assumptions, as Bayesian approaches introduce complexity but offer flexibility and efficiency gains when properly implemented.

The second session focused on the evolving regulatory landscape for Bayesian methods, centering on upcoming guidance from the EMA and the ICH E20 perspective on adaptive designs. Peter van den Ven introduced the development of an EMA concept paper intended to clarify the scope of a future reflection paper on the use of Bayesian statistics in clinical development. While Bayesian methods have been referenced in guidelines since 1998, their use in pivotal trials remains limited. The new guidance aims to establish standards for justification, transparency, and robustness, particularly for applications such as extrapolation, evidence synthesis, and adaptive designs. The presentation highlighted that while Bayesian methods offer flexibility, they necessitate rigorous pre-specification of priors and sensitivity analyses to ensure regulatory confidence.

Frank Bretz and Frank Pétavy provided complementary industry and regulatory perspectives on the draft ICH E20 guideline, which seeks to harmonize global expectations for adaptive clinical trials. The guideline emphasizes that while adaptive designs offer flexibility, they introduce complexity that requires careful planning to control Type I error and maintain trial integrity. Both speakers noted that Bayesian methods, though less harmonized than frequentist approaches, play a critical role in informing adaptations like futility analysis and borrowing external data. However, successfully integrating these methods requires sponsors to clearly justify their choice of priors, document assumptions transparently, and engage in early scientific advice to align with regulators on strategies for managing prior-data conflict and ensuring robust conclusions.

Q&A and discussion

The discussion following the presentations on Bayesian statistics in clinical trials focused on the evolving role of Bayesian methods in regulatory decision-making, their comparison with frequentist approaches, and the practical challenges of implementation. Participants emphasised that Bayesian designs offer intuitive metrics and direct answers to clinical questions, but their adoption requires careful justification due to additional assumptions and the complexity of simulations. While frequentist methods have historically been the default, there was broad agreement that Bayesian approaches should be evaluated on their own merits, guided by the research question and context of use rather than legacy preferences.

A recurring theme was the importance of the context of use, particularly in areas like paediatrics, rare diseases, and personalized medicine, where traditional trial designs may not be feasible. The discussion explored whether borrowing external data should be driven by necessity or opportunity, with some participants calling to avoid narrowing the scope of Bayesian methods to only cases of need.

Communication challenges were also highlighted, both in explaining Bayesian concepts to clinicians and in documenting simulations and assumptions for regulators. Suggestions included developing best practices for transparent reporting and fostering early-stage dialogue between sponsors and regulators to ensure mutual understanding.

Finally, the group advocated an eclectic, question-driven approach to statistical methodology, echoing Sir David Cox’s principle of choosing the best tool for the problem at hand. Rather than framing the conversation as a frequentist versus Bayesian paradigm shift, participants encouraged openness to innovation, supported by robust scientific rationale and clear documentation. The session concluded with recognition of the complexity involved in integrating Bayesian methods into regulatory frameworks and a shared commitment to continued learning and collaboration across pharmaceutical industry, academia, and regulatory bodies.

Session 3

Use cases of Bayesian statistics I

Summary of Session 3

- Bayesian methods without borrowing could be particularly suited for ultrarare disease trials, offering interpretable probability-based decisions, type I error control, and robustness under small-sample constraints.
- Bayesian designs, such as those used in the Glo-BNHL platform trial, enable efficient evaluation of multiple treatments, early stopping for futility, and flexible addition of new arms while addressing regulatory concerns around platform trials.
- Posterior probabilities and predicted probabilities of success provide intuitive metrics for clinicians, supporting transparent and clinically meaningful decision-making compared to frequentist p-values.
- Bayesian methods can naturally handle complexities such as intercurrent events and missing data, while aligning interim and final analyses with clinical reasoning; however, their adoption in pivotal trials requires further regulatory dialogue.

Session 3 explored diverse use cases for Bayesian statistics, demonstrating their utility in challenging clinical contexts such as ultrarare diseases and platform trials. Natalia Muehlemann and Jan Priel presented how Bayesian methods without borrowing can address the constraints of small sample sizes inherent in ultrarare disease research. By using weakly informative priors, their approach improved model convergence and provided direct probability statements, offering a more robust alternative to methods which rely on asymptotic assumptions that fail in small populations. Prof. Lucinda Billingham expanded on this theme with the Glo-BNHL trial, a platform study for rare paediatric cancer. This design employs a Bayesian adaptive framework to independently evaluate multiple treatment arms, using posterior probabilities to guide early stopping for futility or expansion.

The session also addressed the application of Bayesian modelling to more complex trial dynamics, such as handling intercurrent events and interim decision-making. Prof. Nicky Best and Prashant Dalvi presented a case study in chronic pain, highlighting how Bayesian frameworks can align statistical analysis with clinical reasoning. By estimating the probability that a treatment effect exceeds a clinically relevant threshold, rather than just testing for statistical significance, the design provided intuitive metrics for decision-making. Furthermore, the use of predicted probabilities for interim analyses offered a flexible method for assessing futility and handling missing data, demonstrating that Bayesian frameworks can maintain rigorous operating characteristics while delivering superior interpretability and adaptability.

Q&A and discussion

Following the third session, the discussion focused on practical and methodological aspects of using Bayesian designs in clinical trials, particularly for small populations or rare diseases. Participants examined how prior distributions influence interim decisions like stopping for futility or efficacy. While some priors are called "non-informative" (meaning no intention to use prior information), they still carry information that can impact outcomes in data-limited settings. Transparency in prior selection and sensitivity analyses to test robustness were emphasized.

Speakers stressed tailoring priors to the decision context—using skeptical priors to avoid premature efficacy claims, and optimistic ones to fairly assess futility. Predictive probabilities were highlighted as intuitive for clinicians. Operational issues were also discussed, such as pre-specifying fallback strategies and documenting them in analysis plans.

Regulatory representatives outlined expectations for sponsors using Bayesian methods, including clear modelling rationale, prior justification, sensitivity analyses, and reproducible code. The idea of formalising these expectations in future guidance documents was raised. Lastly, participants stated that Bayesian methods offer flexibility and transparency, but require thoughtful design, clear communication, and rigorous evaluation.

Session 4

Use cases of Bayesian statistics II

Summary of Session 4

- The DINAMO study demonstrated how pharmacometrics-enhanced Bayesian borrowing can strengthen evidence in paediatric trials by combining mechanistic modelling with robust MAP priors, while addressing prior-data conflict through sensitivity analyses and conservative weighting.
- Bayesian borrowing approaches can provide meaningful support for underpowered paediatric studies, but require clear justification of assumptions, transparent documentation, and early regulatory engagement to ensure acceptability.
- Regulators recognise the potential of Bayesian methods for paediatric extrapolation but emphasise that determining the appropriate degree of borrowing is complex and must be guided by biological plausibility, multidisciplinary discussion, and traceable decision-making.
- FDA initiatives such as the C3TI Demonstration Program and forthcoming guidance on Bayesian methodology aim to promote innovation and provide a structured pathway for integrating Bayesian approaches into confirmatory trials.

Session 4 examined the use of Bayesian methods to enhance trial efficiency and evidence generation, with a focus on borrowing information across populations and trials. Simon Wandel and Anastasia Lesogor addressed the challenge of demonstrating benefits for key secondary endpoints, such as cardiovascular death, which often remain underpowered in large cardiovascular outcome trials. They proposed a Bayesian dynamic borrowing approach that leverages treatment effect data from adjacent populations across multiple trials. This hybrid design strategy aims to increase power for critical secondary outcomes without inflating Type I error, illustrating how Bayesian methods can complement primary frequentist analyses to provide more robust evidence for clinical decision-making.

The session also delved into paediatric extrapolation, illustrated by the DINAMO study presented by Martin Oliver Sailer and Igor Tartakovsky. Faced with potential underpowering in a paediatric type 2 diabetes trial, the team employed a supplementary Bayesian analysis that combined pharmacometrics modelling with robust Meta-Analytic Predictive priors. This approach allowed for the principled borrowing of adult exposure-response data and historical paediatric data, in order to strengthening the evidence base while managing prior-data conflict through mixture priors.

James Travis provided the regulatory counterpoint, emphasising that while the FDA supports Bayesian extrapolation to improve efficiency, success hinges on strong biological justification and transparent determination of the appropriate degree of borrowing. He highlighted new initiatives like the C3TI Demonstration Program as pathways for sponsors to engage early and align on these complex methodological choices.

Q&A and discussion

The discussion focused on the use of Bayesian and pharmacometric approaches for incorporating external information into clinical trial designs, particularly in the context of rare events and paediatric extrapolation. Participants reflected on the FDA's updated Bayesian Statistical Analysis (BSA) Demonstration Project, and noted that while early uptake was limited, recent changes may encourage broader engagement.

A key theme was the distinction between rare populations and rare events. While both present feasibility challenges for evidence generation, rare events often occur in data-rich environments, which can make borrowing more feasible. Participants discussed the potential for using aggregate data from published studies when individual patient data is unavailable, provided the data quality is sufficient. Regulators emphasised the importance of early dialogue and careful justification when proposing such approaches.

The DINAMO study involving paediatric type 2 diabetes was used to illustrate how exposure-response modeling and Bayesian priors can be combined. The approach included covariate adjustments, such as weight, and a robust component to mitigate the risk of over-reliance on adult data. The effective sample size of the prior was deliberately limited to avoid overwhelming the small paediatric dataset. The discussion also noted that the strength of the approach may depend on the context and the nature of the uncertainty being addressed.

Participants raised questions about how differences in disease progression between adults and children were handled, particularly when placebo responses diverged. It was acknowledged that while some adolescent data were included, certain assumptions may not have been fully captured in the models. Regulators reiterated that the level of paediatric data required depends on the degree of uncertainty and the specific knowledge gaps being addressed. The discussion concluded with a recognition that both modeling approaches can be valuable, but their application must be tailored to the clinical and evidentiary context.

Session 5

Use cases of Bayesian statistics III

Summary of Session 5

- Bayesian shrinkage methods using hierarchical models improve the reliability of subgroup treatment effect estimates by reducing variance and mean squared error, outperforming conventional approaches in predictive accuracy.
- These methods assume partial exchangeability across subgroups, allowing estimates to shrink toward the overall effect when subgroup-specific evidence is weak, which enhances interpretability and clinical decision-making.
- Communication challenges remain, including clarifying the concept of "shrinkage" and ensuring transparency about assumptions; regulators recognised the potential of complementing standard subgroup analyses with Bayesian shrinkage estimates in trial reports and labelling.
- ICH-M15 provides a structured framework for planning, evaluating, and submitting Bayesian models, emphasizing transparency, risk assessment, and early regulatory dialogue to ensure robust and acceptable implementation in confirmatory settings.

Session 5 focused on advanced applications of Bayesian methods for subgroup analyses and model assessment, illustrating how these tools can refine estimation and structure regulatory submissions. Simon Wandel and John McMurray presented Bayesian shrinkage methods as a solution to the instability and high variability often seen in conventional subgroup analyses. By using hierarchical models that assume partial exchangeability, these methods allow subgroup estimates to "shrink" towards the overall treatment effect, thereby reducing mean squared error and improving predictive accuracy. The speakers argued that complementing standard forest plots with shrinkage estimates can provide more reliable and interpretable data for clinical decision-making, addressing the common pitfalls of over-interpreting noisy subgroup findings.

Tobias Mielke introduced the ICH M15 guideline as a systematic framework to support Model-Informed Drug Development (MIDD), examining its specific relevance to Bayesian modelling. Using a case study on dynamic borrowing for overall survival analysis, which was ultimately rejected by regulators, the presentation highlighted the critical need for a structured assessment process. ICH M15 emphasizes transparency in defining the context of use, rigorously evaluating model risk, and validating assumptions. The session concluded that while Bayesian methods may offer significant advantages, their regulatory acceptance depends on following such systematic frameworks to clearly articulate risks, justify assumptions, and ensure robust validation through early dialogue.

Q&A and discussion

The discussion focused on the application of a proposed framework for Bayesian dynamic borrowing in clinical trials, particularly in the context of evaluating treatment effects such as overall survival. Participants acknowledged the framework's potential as a communication tool between industry and regulators, emphasizing its flexibility and relevance across various types of submissions. While one participant suggested the presented case was an ideal example for applying Bayesian dynamic borrowing, regulators responded cautiously, noting that a full assessment would require a complete picture of the design and supporting evidence. The importance of evaluating such methods was emphasised not only at the analysis stage but also during trial design and there was a call for a more structured framework to assess credibility throughout the process.

Concerns were raised about the risk of making incorrect claims and the implications such claims could have if included in product labelling. Regulators stressed the importance of the information in the Summary of Product Characteristics (SmPC), as it may directly influence clinical decisions on the use of medicinal products. In response, participants highlighted the importance of supporting such claims with multiple layers of evidence, including sensitivity analyses and robust modeling approaches. The discussion also touched on the limitations of current regulatory interactions, such as the time constraints of scientific advice meetings, and the need for more flexible and ongoing dialogue to evaluate complex statistical methods.

There was also support for the use of Bayesian shrinkage methods to address issues with small subgroups and wide confidence intervals, which are common challenges in interpreting forest plots. Participants noted that such methods could reduce unnecessary debate and improve clarity in subgroup analyses. The conversation concluded with reflections on the broader implications of evidence synthesis. It was suggested that the Bayesian framework offers a valuable opportunity to formalise how evidence is integrated, and uncertainties are communicated. Regulators emphasised the need to distinguish between formal claims and reliable supporting information, especially when such information may be included in product labelling. They acknowledged that clearer standards are needed to determine when supporting evidence is sufficiently reliable to enable decision-making, and that this should be an area for continued discussion.

Summary and take-home message

Summary of closing remarks by Peter Arlett (EMA)

The closing remarks highlighted a highly productive day focused on Bayesian statistics in clinical development. The need to accelerate the path from innovation to safe and effective medicines was emphasised, particularly in areas of unmet medical need. A key takeaway was that methodology should be driven by the research question, ensuring flexibility in trial design and methods as long as they are scientifically rigorous.

While Bayesian approaches offer significant potential, they may be perceived as more complex and less transparent, which can hinder trust among clinicians, regulators, and the public. Building understanding and confidence in these methods is essential, requiring targeted communication, stakeholder engagement, and structured training across regulators, medicine developers, and patient groups.

Peter Arlett stressed the need for clear guidance, referencing the upcoming EU guidance on Bayesian statistics and the draft ICH E20 guideline on adaptive designs. Beyond guidance, a change management approach was recommended to integrate Bayesian methods into mainstream clinical development where considered appropriate, rather than limiting them to niche applications.

The remarks concluded with a call for collaboration to deliver better medicines faster, combining methodological innovation with transparency and education to unlock the full potential of Bayesian approaches.

Appendix 1. List of speakers and session chairs

Peter Arlett	EMA
Marianne Lunzer	AGES
Kristin Karlsson	MWP vice-chair, Swedish Medical Products Agency (MPA)
Frank Pétavy	EMA
Aysun Cetinyurek Yavuz	MEB-CBG
Annette Kopp- Schneider	German Cancer Research Center (DKFZ)
Nicky Best	EFPIA/EFSPI
Martin Posch	Medical University of Vienna
Juan Jose Abellan	EMA
Peter van den Ven	MEB-CBG
Frank Bretz	EFPIA/EFSPI
Tobias Fellinger	AGES
Florian Lasch	EMA
Natalia Muehlemann	EFPIA/EFSPI
Jan Priel	EFPIA/EFSPI
Lucinda Billingham	University of Birmingham
Prashant Dalvi	EFPIA/EFSPI
Simon Wandel	EFPIA/EFSPI
Anastasia Lesogor	EFPIA/EFSPI
Martin Oliver Sailer	EFPIA/EFSPI
Igor Tartakovsky	EFPIA/EFSPI
James Travis	FDA
Manolis Efthymios	EMA
Björn Bornkamp	EFPIA/EFSPI
John McMurray	University of Glasgow
Tobias Mielke	EFPIA/EFSPI

Appendix 2. Acronyms

ACT-EU	Accelerating Clinical Trials in the EU
AGES	Austrian Agency for Health and Food Safety
BDB	Bayesian dynamic borrowing
CTCG	Clinical Trials Coordination Group
C3TI	CDER Center for Clinical Trial Innovation
DKFZ	German Cancer Research Center
EFPIA	European Federation of Pharmaceutical Industries and Associations
EFSPI	European Federation of Statisticians in the Pharmaceutical Industry
EMA	European Medicines Agency
FDA	Food and Drug Administration
ICH	International Council for Harmonisation
MEB-CBG	Dutch Medicines Evaluation Board
MWP	Methodology Working Party
T1E	Type 1 Error
T2D	Type 2 Diabetes
UMP	uniformly most powerful
Q&A	Questions and Answers

Appendix 3. Presentation summaries

1. Introduction to Bayesian statistics and decision making

Bayesian borrowing in clinical trial test decisions: Frequentist type I error rate and power

Annette Kopp-Schneider (German Cancer Research Center, Heidelberg)

The presentation examined the implications of Bayesian borrowing in clinical trials, focusing on its effect on frequentist operating characteristics such as type I error (T1E) and power. It began by outlining how Bayesian hypothesis testing incorporates prior information, including external data, into the decision-making process. While this can improve efficiency, it introduces challenges in maintaining strict T1E control, which is a regulatory requirement. The speaker emphasized that when a uniformly most powerful (UMP) test exists, no borrowing approach can increase power under frequentist evaluation, regardless of the method used.

A key part of the discussion addressed hybrid control arm trials, where external control data are adaptively borrowed to supplement current control data. The analysis showed that borrowing can lead to T1E inflation if not properly calibrated. To ensure fair comparison, the presentation proposed calibrating the non-borrowing test to match the T1E of the borrowing test. Results indicated that, under strict frequentist criteria, borrowing typically does not yield power gains and may even result in slight power loss. However, potential benefits arise if assumptions about similarity between current and external data are accepted, moving beyond the frequentist framework. In such cases, Bayesian metrics and decision-theoretic approaches can provide meaningful advantages, particularly when prior-data conflict is minimal. The session concluded that while borrowing offers conceptual appeal, its practical benefit under frequentist constraints is limited, and careful calibration and transparency are essential for regulatory acceptability.

Opportunities and challenges of using Bayesian Methods to support regulatory decision making

Summary presentation of Nicky Best (EFPIA/EFSPI)

The presentation explored the opportunities and challenges of using Bayesian methods to support regulatory decision-making. It began by noting that despite their advantages, adoption in confirmatory trials remains limited due to barriers such as lack of familiarity among researchers and absence of clear regulatory guidance. Bayesian approaches are already widely used for internal decision-making, safety monitoring, early-phase trials, and medical devices, and their relevance is growing with the increasing complexity of drug development, rare disease studies, and availability of high-quality real-world data.

Key motivations for Bayesian methods include their ability to provide direct probabilities for treatment effects, facilitate interim decisions such as futility or dose selection, and support conditional approvals in high unmet-need settings. They also enable formal evidence synthesis, integration of prior knowledge, and consistency between imputation and final analyses. However, these benefits come with added complexity: subjective choices about priors and hyperparameters require transparency and early dialogue between sponsors and regulators. The presentation emphasized that while assumptions are also present in frequentist designs, the Bayesian framework encourages structured discussion and documentation upfront.

A case example illustrated Bayesian dynamic borrowing (BDB) in rare disease trials, highlighting both its potential and the need for regulatory clarity on acceptable assumptions for

extrapolation. Type I error control remains a critical issue, particularly for borrowing designs, where strict frequentist calibration often eliminates power gains. Alternative evaluation metrics, such as average Type I error over plausible parameter ranges, were proposed. The session concluded that Bayesian methods are scientifically rigorous and increasingly essential, but successful implementation depends on education, robust methodological frameworks, and early multi-stakeholder alignment on design choices and prior-data assumptions.

2. Upcoming Guidance – Challenges and Opportunities

EU Concept Paper on the use of Bayesian statistics in clinical development

Summary presentation of Peter van de Ven (MEB-CBG)

The presentation outlined the development of an EMA concept paper on the use of Bayesian statistics in clinical development, aimed at providing regulatory clarity and guidance. While Bayesian methods have been mentioned in ICH E9 since 1998 and in several EMA and ICH guidelines, their application in pivotal trials remains limited. Current regulatory practice relies primarily on frequentist approaches with strict type I error control, and Bayesian methods are mainly seen in paediatric extrapolation, pharmacometrics, and early-phase studies. The concept paper will present the proposed scope of a planned reflection paper that should provide guidance on when and how Bayesian approaches should be justified and can be considered robust enough for regulatory decision-making.

Potential applications include extrapolation across populations, dynamic borrowing of external data, evidence synthesis, adaptive designs, and handling of missing data. However, the presentation emphasized key challenges: the need for clear justification of Bayesian elements, pre-specification of priors and models, and sensitivity analyses to demonstrate robustness. Additional complexities include managing prior-data conflict, ensuring transparency, and dealing with scenarios where type I error control is not feasible. The reflection paper will provide guidance on required information, justification, and reporting standards, covering topics such as non-informative and informative priors, adaptive Bayesian designs, and pharmacometrics modelling. It will also stress the importance of early engagement with regulators to align on assumptions and methodological choices. The overarching goal is to enable the appropriate and transparent use of Bayesian methods while maintaining confidence in benefit-risk assessments for regulatory decisions.

ICH E20 – an industry perspective

Summary presentation of Frank Bretz (EFPIA/EFSPI)

The presentation introduced the ICH E20 guideline on adaptive designs for confirmatory clinical trials, developed to harmonize global regulatory expectations and address inconsistencies across existing national guidelines. Adaptive designs allow prospectively planned modifications based on interim data, offering flexibility but also introducing additional complexity and uncertainty compared to traditional designs. The guideline emphasizes key principles such as adequacy within the development program, rigorous trial planning, control of Type I error, reliability of estimation, and maintenance of trial integrity.

A dedicated section addresses the use of Bayesian methods, which remain less harmonized and require justification. While Bayesian approaches can inform adaptations, such as futility stopping rules, or enable borrowing of external data through informative priors, they raise challenges including prior-data conflict, risk of bias, and maintaining error control. Sponsors are expected to pre-specify priors, decision criteria, and adaptive elements, conduct simulations under

various scenarios, and perform sensitivity analyses to ensure robustness. Documentation of prior sources and transparency in assumptions are critical.

The guideline concludes that adaptive designs, with or without Bayesian methods, can be appropriate when carefully planned and justified. However, Bayesian applications demand additional scrutiny to ensure regulatory confidence in benefit-risk assessments. Public consultation is invited to clarify circumstances where Bayesian methods satisfy core principles and can support regulatory decision-making.

ICH E20 – a regulatory perspective

Summary presentation of Frank Pétavy (EMA)

The presentation provided a regulatory perspective on the ICH E20 guideline, which aims to harmonize the use of adaptive designs in confirmatory clinical trials. EMA emphasized that ICH guidelines, while not legally binding, represent harmonized community positions and strongly influence regulatory assessment. Applicants are expected to follow these guidelines or justify any deviations, ideally through early scientific advice.

E20 defines adaptive designs as trials allowing prospectively planned modifications based on interim analyses, including futility assessments. Its scope is broader than previous EMA reflections, covering a wide range of adaptations such as sample size re-estimation and treatment arm selection, provided Type I error control is maintained. The guideline also addresses Bayesian methods, which may be used for adaptations like futility stopping or historical borrowing, but only when their use is clearly justified and conclusions remain robust, as required by ICH E9.

A key focus was on linking E9 principles with E20, particularly for Bayesian borrowing. While Bayesian approaches can enhance flexibility, they introduce challenges such as prior-data conflict, the need for dynamic borrowing strategies, and ensuring clinical relevance of historical data. The presentation highlighted the importance of planning discussions with clinical assessors early, pre-specifying assumptions, and considering mitigation strategies for prior-data conflict. An example illustrated complexities in combining historical and current control data, underscoring the need for transparency and sensitivity analyses.

The session concluded that regulatory recommendations should remain method- and framework-agnostic, while recognizing that some adaptations may benefit from Bayesian approaches. However, using Bayesian methods for regulatory decision-making beyond adaptive designs requires further development and dialogue.

3. Use cases of Bayesian statistics I

Bayesian methods without borrowing in ultrarare diseases

Summary presentation of Natalia Muehlemann (EFPIA/EFSPI) and Jan Priel (EFPIA/EFSPI)

The presentation focused on the application of Bayesian methods without borrowing in the context of ultrarare diseases, where conventional trial designs face significant challenges due to extremely small patient populations. Traditional powering is often infeasible, leading to underpowered studies and funding difficulties. The speakers highlighted that adaptive and model-based approaches are essential to improve efficiency and interpretability in such settings.

A case study illustrated a trial with approximately 50 patients and an event count outcome analysed using a negative binomial model. Bayesian methods were motivated by their ability to

provide direct probabilities of treatment effect, facilitate interim decision-making, and address limitations of frequentist approaches, which rely on asymptotic assumptions often violated in small samples. The design incorporated weakly informative priors to regularize models, improve convergence, and maintain type I error control while preserving power.

Simulation results demonstrated that Bayesian designs achieved comparable power to frequentist designs but with better type I error control and interpretability. Posterior distributions and credible intervals offered clinically meaningful insights, while frequentist p-values provided limited decision-making value. The approach also supported early stopping for efficacy through group sequential design, enhancing trial efficiency.

The presentation concluded that Bayesian methods are particularly suited for ultrarare disease trials, offering robustness, flexibility, and transparency in decision-making. They enable reliable inference under small-sample constraints and can improve regulatory confidence when assumptions and priors are clearly justified, and sensitivity analyses are performed.

Bayesian adaptive design for a practice-changing platform trial in a rare paediatric cancer: The Glo-BNHL Trial

Summary presentation of Lucinda Billingham (University of Birmingham)

The presentation described the Glo-BNHL trial, a global platform study evaluating novel agents in children and adolescents with relapsed or refractory B-cell non-Hodgkin lymphoma, a rare and heterogeneous cancer with very limited treatment options. Given the small patient population, around 30 patients per year worldwide, the design aimed to maximize efficiency while minimizing exposure to ineffective therapies. The trial uses a Bayesian adaptive framework with multiple treatment arms, each assessed independently without a control arm, and a two-stage design allowing early stopping for futility or expansion based on interim results.

The statistical approach employs a beta-binomial model with minimally informative priors to estimate response rates and calculate posterior probabilities. Decision-making is based on predefined thresholds: a "Go" decision requires a posterior probability above 0.80 at interim (based on 15 patients) and 0.95 at confirmatory analysis (30 patients). Interim analyses also use predicted probabilities of success to guide continuation or early termination. This approach enables cumulative learning, flexibility in adding new arms, and efficient evaluation of promising therapies.

Examples illustrated how Bayesian methods provide intuitive metrics, such as the probability that the true response rate exceeds a clinically relevant target, which are easier for clinicians and regulators to interpret than frequentist p-values. Operating characteristics confirmed control of type I error and adequate power, while simulations demonstrated the benefits of multiple interim analyses for patient safety and resource use. The design has undergone EMA and FDA consultations, with feedback incorporated into the protocol.

The presentation concluded that Bayesian adaptive designs are particularly suited for rare paediatric cancers, offering transparency, flexibility, and clinically meaningful decision-making, while supporting regulatory confidence through rigorous planning and sensitivity analyses.

Bayesian modelling to handle intercurrent events and facilitate interim decision making

Summary presentation of Nicky Best (EFPIA/EFSPI) and Prashant Dalvi (EFPIA/EFSPI)

The presentation explored how Bayesian methods can enhance clinical interpretation, interim decision-making, and handling of intercurrent events in chronic pain trials, using a Phase 2

randomized, placebo-controlled study as a case example. Chronic pain studies face challenges such as high placebo variability and frequent Phase 3 failures despite statistical significance, underscoring the need for designs that prioritize clinically meaningful effects.

The Bayesian approach was contrasted with conventional frequentist methods. While both controlled type I error and achieved similar power, Bayesian designs provided additional insights by estimating the probability that the true treatment effect exceeds clinically relevant thresholds (e.g., minimal clinically important difference). This allowed decision-making to align more closely with clinical reasoning rather than relying solely on p-values. Posterior probabilities offered interpretable metrics, such as the probability that the treatment effect exceeds 0.5 or 1 unit on the pain scale.

Interim analyses were framed as prediction problems, using Bayesian predicted probabilities of end-of-trial 'success' to guide futility decisions. This approach naturally accommodates partial data and complex scenarios, offering greater flexibility than conditional power calculations in frequentist designs. For intercurrent events such as treatment discontinuation or prohibited medication use, Bayesian models handled missing data through priors, avoiding the need for separate multiple imputation and simplifying analysis.

The proposed fully Bayesian framework can deliver pre-specified frequentist operating characteristics while providing clinically intuitive decision rules and robust handling of missing data. The presentation concluded by posing the question of whether such designs could be acceptable in pivotal Phase 3 trials, given their potential to improve interpretability, efficiency, and alignment with clinical objectives.

4. Use cases of Bayesian statistics II

Leveraging information for a key secondary endpoint across adjacent populations

Summary presentation of Simon Wandel (EFPIA/EFSPI) and Anastasia Lesogor (EFPIA/EFSPI)

The presentation addressed the challenge of demonstrating benefits for less frequent cardiovascular endpoints, such as cardiovascular death, in outcome trials. These trials are typically large, lengthy, and powered for composite primary endpoints like major adverse cardiovascular events (MACE), leaving key secondary endpoints underpowered despite their clinical importance. Contemporary lipid-lowering studies have shown limited evidence of mortality benefit, partly due to delayed treatment effects and declining event rates from improved background therapy.

Traditional solutions, such as open-label extensions, provide long-term data but face interpretational limitations due to lack of control arms and selective continuation. To overcome these challenges, the speaker proposed a Bayesian dynamic borrowing approach that leverages information from adjacent populations across multiple trials. This method focuses on treatment effects rather than control data, adapts to population differences, and conceptually aligns with meta-analysis, making it easier to communicate to non-statisticians.

Design evaluations showed that borrowing information can substantially increase power for secondary endpoints (e.g., from ~50% to ~79%) without inflating type I error. The approach also considers case scenarios where conflicting results between trials require careful interpretation. The conclusion emphasized moving beyond a binary frequentist-versus-Bayesian view toward hybrid designs, combining frequentist primary analyses with Bayesian methods for secondary endpoints. Such flexibility could generate robust evidence for clinically relevant outcomes and accelerate decision-making in cardiovascular drug development.

Bayesian borrowing for paediatric extrapolation: the DINAMO study

Summary presentation of Martin Oliver Sailer (EFPIA/EFSPI) and Igor Tartakovsky (EFPIA/EFSPI)

The presentation discussed the DINAMO trial, which evaluated empagliflozin and linagliptin in children and adolescents with type 2 diabetes (T2D), addressing the lack of oral treatment options beyond metformin and insulin. The trial faced potential underpowering due to high variability in HbA1c change, prompting a supplementary Bayesian analysis to leverage historical data and improve inference without reopening recruitment.

The Bayesian approach combined pharmacometrics modelling and robust meta-analytic predictive (MAP) priors. Pharmacometrics-based borrowing used adult exposure–response data to inform priors under the assumption of conditional exchangeability after adjusting for exposure differences. Additional analyses applied robust MAP priors using paediatric data from medicines with similar mechanisms of action, mitigating risks of prior-data conflict. Mixture priors were constructed with expert-elicited weights and variance constraints to ensure conservative borrowing.

Results showed that the primary frequentist analysis confirmed significant efficacy for empagliflozin but not for linagliptin. Bayesian borrowing reinforced evidence for empagliflozin (posterior mean –0.945% HbA1c, probability of superiority >0.999) and provided supportive evidence for linagliptin (posterior mean –0.514%, probability 0.982), despite its non-significant frequentist result. Sensitivity analyses assessed robustness to prior assumptions and potential conflicts.

The presentation concluded that pharmacometrics-enhanced Bayesian borrowing offers a powerful strategy for paediatric extrapolation, combining mechanistic modeling with dynamic borrowing to strengthen evidence in small populations. This approach, aligned with regulatory engagement, demonstrates how Bayesian methods can address feasibility challenges in paediatric drug development while maintaining rigor and transparency.

A Regulator's Perspective on Paediatric Bayesian Methods

Summary presentation of James Travis (FDA)

The presentation provided a regulatory perspective on the use of Bayesian methods in paediatric medicine development, emphasizing their role in extrapolation and trial efficiency. Paediatric extrapolation has long been part of regulatory practice, allowing adult efficacy data to inform paediatric labelling when disease and treatment effects are sufficiently similar. Bayesian approaches formalize this process by explicitly incorporating prior knowledge and quantifying uncertainty, but they require strong biological justification for assuming similarity between populations.

A case study in paediatric type 2 diabetes highlighted challenges with traditional designs: high variability in paediatric patients led to underpowered trials despite adequate planning, and placebo responses differed from adults. Retrospective analyses suggested that borrowing information from adult data could have improved decision-making, prompting FDA to recommend Bayesian analyses for future paediatric T2D programs. However, determining the appropriate degree of borrowing remains the most difficult aspect, requiring multidisciplinary discussion, transparent metrics, and sensitivity analyses to address prior-data conflict.

The presentation also outlined FDA's initiatives to support innovation, including the C3TI Demonstration Program, which promotes early engagement on Bayesian statistical analysis and other novel approaches. This program aims to build experience with Bayesian methods in Phase

3 trials and ensure alignment on statistical plans. Additionally, FDA plans to issue draft guidance on the use of Bayesian methodology in clinical trials.

The key message was that Bayesian methods can enhance efficiency and interpretability in paediatric trials, but their success depends on rigorous justification, clear communication, and early regulatory interaction.

5. Use cases of Bayesian statistics III

Bayesian shrinkage methods for routine estimation of subgroup treatment effects

Summary presentation of Björn Bornkamp (EFPIA/EFSPI) and John McMurray (University of Glasgow)

The presentation addressed the use of Bayesian shrinkage methods for estimating subgroup treatment effects, a critical issue given the growing interest in treatment effect heterogeneity and the limitations of conventional subgroup analyses. Traditional approaches often fail due to small sample sizes and multiplicity, leading to unstable and non-replicable findings. Bayesian shrinkage offers a solution by borrowing strength from the overall population to stabilize subgroup estimates, reducing variance while maintaining interpretability.

The method relies on hierarchical models that assume partial exchangeability across subgroups, allowing estimates to shrink toward the overall effect when subgroup-specific evidence is weak. This approach improves the bias–variance trade-off and reduces mean squared error compared to conventional estimates. Examples, such as from the SURPASS-2 trial, illustrated how Bayesian shrinkage produces more consistent and credible subgroup estimates than standard forest plots.

Simulation studies and benchmarking on Phase 3 trial data demonstrated that shrinkage models outperform conventional methods in predictive accuracy, even under heterogeneous treatment effects. Various shrinkage priors, including hierarchical and alternative models like the so-called horseshoe and R2D2, were evaluated, with results showing consistent gains in predictive performance. However, the presentation acknowledged challenges in communication, such as the perception of "shrinkage" and the need to clarify assumptions about exchangeability.

The key recommendation was to complement standard subgroup analyses in clinical trial reports and labelling with Bayesian shrinkage estimates, enhancing reliability and clinical decision-making. This approach aligns with regulatory guidance encouraging robust, transparent methods for subgroup evaluation.

Application of ICH-M15 for Bayesian Modelling - Using a systematic model assessment framework to support design submission and discussion

Summary presentation of Tobias Mielke (EFPIA/EFSPI)

The presentation introduced ICH-M15 as a structured framework to support model-informed drug development (MIDD) and explored its relevance for Bayesian modelling in regulatory submissions. Using a case study on overall survival (OS) data borrowing in multiple myeloma trials, the speakers highlighted challenges in implementing Bayesian dynamic borrowing across parallel programs. While the approach aimed to improve efficiency by leveraging overlapping control data, regulators rejected its use as a primary analysis due to concerns about uncontrolled population differences, post-progression treatments, and inflated false-positive risk.

ICH-M15 proposes a systematic assessment process for modelling approaches, emphasizing transparency in defining the problem, context of use, assumptions, and model influence on

decision-making. Key elements include evaluating model risk and impact, considering consequences of wrong decisions, and specifying verification and validation steps. For Bayesian borrowing, this involves pre-specifying sensitivity analyses, setting limits on the weight of borrowed data, and ensuring type I error control under plausible scenarios. The framework also encourages early regulatory dialogue to align on technical criteria and optimize study design for model applicability.

The discussion underscored that while Bayesian methods can enhance efficiency and interpretability, their acceptability depends on rigorous justification, clear articulation of risks, and robust evaluation plans. ICH-M15 could provide a common language for these discussions, improving consistency and confidence in submissions involving Bayesian approaches.

Appendix 4. Q & A

This appendix includes a few selected questions posed during the presentations and subsequent discussions for which answers were provided.

Question 1

Question (from susanne.urach@ages.at):
Bayesian methodology is often not used because of the additional assumptions needed for type I error control. Would you also recommend Bayesian approaches when frequentist methodology is also feasible?

Answer (from Anonymous):
Oh yes there are many uses of Bayesian methods that add value even when calibrated to control type-1 error over the null space. Examples include: arm dropping or response adaptive randomization based on the Bayesian probability that each treatment arm is the best, imputation of missing information, borrowing across groups, fitting dose response / toxicity response models.

Question 2

Question (from burak-kuersad.guenhan@merckgroup.com):
@Nicky Best: When we have strict type 1 error control rate in a Bayesian framework, do we still have the added value of Bayesian methodology? Would not be an easier solution is simply to use frequentist methods when strict type 1 error rate is needed?

Answer (from nicky.x.best@gsk.com):
The case studies presented in session 3 illustrated several potential benefits/added value of using a Bayesian design even when no prior information is borrowed and type 1 error is strictly controlled - including ability to base decision criteria (for interim and end of study) on easily interpretable criteria aligned with clinical reasoning; use of predictive probabilities for interim decision making, and use of weakly informative priors to improve computational stability of estimates in sparse data settings.

Question 3

Question (from susanne.urach@ages.at):
When using Bayesian methods clinical trials/information is not independent anymore/stand on their own. How is the dependence considered for benefit risk evaluation?

Answer (from Anonymous):
Don't conflate Bayesian methods and Bayesian borrowing. Bayesian borrowing is just one use of the Bayesian method, there are many uses of the Bayesian method that do not involve borrowing prior data.

Question 4

Question (from Jixian.Wang@bms.com):
Do we need to specify design prior and analysis prior, at which stage?

Answer (from nicky.x.best@gsk.com):
Both the design and analysis prior should be pre-specified at the design stage. The design prior is only used at the design stage, whereas the analysis prior is used at both the design and analysis stage. The analysis prior is the prior distribution that summarises the external data that is to be borrowed in the analysis of the new trial. The design prior is used only to inform the assumptions about the true parameter values (e.g. true control response; true treatment effect) to be used for evaluating operating characteristics (it does not play any role in the data analysis). The design prior can be different to the analysis prior, and should reflect the range of scenarios we wish to focus on to understand the risks (e.g. of false positives) and benefits (e.g. power/precision) of the proposed design.

Question 5

Question (from lou.whitehead@novartis.com):
Is there any regulatory perspective / mention in the new E20 guideline on the acceptability of historical borrowing on treatment effect data (i.e., difference between treatment and placebo control arms)? (as opposed to borrowing only on control)

Answer (from frank.bretz@novartis.com):
No, we don't talk specifically about this, as it is felt to be out of scope for a guideline on adaptive designs and should be contained in a dedicated guideline on Bayesian methods

European Medicines Agency

Domenico Scarlattilaan 6
1083 HS Amsterdam
The Netherlands

Telephone +31 (0)88 781 6000
Send a question **www.ema.europa.eu/contact**

www.ema.europa.eu

Workshop on the use of Bayesian statistics in clinical development