Contribution ID: 471795b5-170b-4a5f-a815-96bd8ba11436
Date: 16/09/2024 16:15:03

Submission of comments on Methodology Working Party Workplan (MWP) 2025-2027

Fields marked with * are mandatory.

Introduction to the survey on submission of comments on Methodology Workplan 2025-2027

Please click on the link below to download the draft MWP Workplan 2027-2027.
Methodology_Working_Party_Workplan_2025-2027_-_Draft.pdf

The public consultation is launched on 29 July 2024 until 30 September 2024 11:59 pm, CET.

Submissions before 16 September are strongly encouraged as the MWP will like to take the opportunity to discuss comments at their face-2-face meeting on 19&20 September 2024.

Those participating in the consultation are asked to please submit comments via the EU Survey tool, by using the specific table for each section. Please note that login is not required to fill in the survey.

If you respond on behalf of a company that is affiliated with an EU (trade) industry organisations, you are encouraged to share your comments to the respective affiliated EU (Trade) Industry organisation.

Before submission, a draft of the comments can be saved in the EU Survey tool. Once submitted, comments can be edited (by the deadline) by clicking on "Edit contribution" in the link https://ec.europa.eu/eusurvey/ and entering your ID contribution that can be found on the pdf copy of your submission sent via email.

You are invited to provide your organisation or name, country and email address below for the purpose of this consultation (for further information, please see EMA's Data Protection Statement below).

Data Protection Statement

EMA Privacy Statement

All personal data provided within this survey questionnaire will be processed in accordance with Regulation (EU) 2018/1725 on the protection of individuals regarding the processing of personal data by the Union institutions and bodies on the free movement of such data.

This data protection statement provides details on how the Agency, in its capacity as data controller, will process the information that you have given in your questionnaire.

Internally, an 'Internal Controller' has been appointed to ensure the lawful conduct of this processing operation. The contact details of the Internal Controller are the following: Datacontroller. HumanMedicines@ema.europa.eu

Collection of data

EMA will collect all the personal data in this questionnaire, such as your name, organisation, your view on the topics subject to the survey, country of residence and your contact details. Please do not reveal any other personal data in the free text fields. EMA does not directly intend to collect personal data but to use the aggregated data for the purpose of this survey.

For the collection of data in this survey, EMA relies on the EU Survey external system. For more information on how EU Survey processes personal data, please see: https://ec.europa.eu/eusurvey/home/privacystatement

The EU Survey external system uses:

- Session "cookies" to ensure communication between the client and the server. Therefore, user's browser must be configured to accept "cookies". The cookies disappear once the session has been terminated.
- Local storage to save copies of the inputs of a participant to a survey to have a backup if the server is not available during submission or the user's computer is switched off accidentally or any other cause.
- The local storage contains the IDs of the questions and the draft answers.
- IP of every connection is saved for security reasons for every server request.
- Once a participant has submitted one's answers successfully to the server or has successfully saved a draft on the server, the data is removed from the local storage.

Your consent to the processing of your data

When you submit this questionnaire, you consent that EMA will process your personal data provided in the questionnaire as explained in this data protection statement. You may also withdraw your consent later at any time. However, this will not affect the lawfulness of any data processing carried out before your consent is withdrawn.

Start of data processing

EMA will start processing your personal data as soon as the questionnaire response is received.

Purpose of data processing

The purpose of the present data processing activity is to collect the views of stakeholders and/or concerned individuals in relation to the subject-matter of the survey. Your personal data may be used to contact you in relation to the feedback you have provided in response to the survey. No further processing of your personal data for any other purposes outside the scope of this specific context is envisaged.

Location of data storage

All data is stored within a secure data centre at the EMA premises which is password protected and only available to EMA staff members.

Publication of data

The following data collected in this questionnaire will be published on the EMA website at the time of issuing the final guideline subject to this survey:

- organisation name (the entity on behalf you respond to this survey)
- or your name (only if you do not respond to the survey on behalf of an organisation)
- your view/comments on the topics concerned

Country information and your email address will not be published.

Retention period

If you complete and submit this survey, your personal data will be kept until the results have been completely analysed and utilised. Your personal data will be deleted by EMA at the latest 5 years after the questionnaire response was submitted. The file of the data as published will remain stored for archiving purposes beyond the maximum 5 years-retention time of the submitted questionnaire responses.

Your rights

You have the right to access and receive a copy of your personal data processed, as well as to request rectification or completion of these data. You may also request erasure of the data or restriction of the processing in accordance with the provisions of Regulation (EU) 2018/1725. You can exercise your rights by sending an e-mail to Datacontroller.HumanMedicines@ema.europa.eu.

Complaints

If you have any complaints or concerns about the processing of your personal data, you can contact EMA's Data Protection Officer at dataprotection@ema.europa.eu.

You may also lodge a complaint with the European Data Protection Supervisor: edps@edps.europa.eu.

* Please confirm that you have read and understood the Data Protection Statement above and that you consent to the processing of your personal data.
  - (●) Yes
  - ( ) No

* Please confirm that you consent to possibly be contacted by EMA in relation to your survey responses to support the finalisation of the document subject this EU Survey.
  - (●) Yes
  - ( ) No

* Please confirm that you consent to the publication of your organisation name, your name (only if you do not respond to the EU Survey on behalf of an organisation) and your survey responses on the EMA website at the time of issuing the final guideline subject to this survey.
  - (●) Yes
  - ( ) No

Should you not want to give consent to publish, please send your objections to Datacontroller. HumanMedicines@ema.europa.eu.

Please be aware that the sender of the comments is responsible to not disclose any personal data of third parties in the comments.

When you have filled in the EU Survey, please use the submission button at the end of the form to submit the comments to the European Medicines Agency.

For additional information, please consult EMA's privacy statement.

Contributor details

* 1. First name

Katarina

* 2. Last name

Nedog

* 3. Professional email address

katarina.nedog@efpia.eu

* 4. Professional affiliation

EFPIA

5. Are you commenting on behalf of an organisation or stakeholder group, then please indicate the name and email of the main contact point (if it differs from the provided above)

- (●) Yes
- ( ) No

5.1. Name main contact point

Katarina Nedog

5.2. Email address main contact point

katarina.nedog@efpia.eu

6. Your area of expertise

- [x] Biostatistics
- [ ] Real World Evidence
- [ ] Clinical Pharmacology (PK/Modelling and Simulation)
- [ ] Artificial Intelligence and Data Science

- [ ] Pharmacogenomics

6.1. Other are of expertise - please specify

7. What type of stakeholder would you consider yourself

- [ ] Academia
- [x] Industry
- [ ] Healthcare professional
- [ ] Individual
- [ ] Patient and consumer

7.1. Other - please specify

1. General comments on the Workplan

1. General comments on the Workplan

	Stakeholder name (to be repeated in all rows to facilitate extraction and identification of comments, thank you.)	General comment
1	EFPIA	Completion of the proposed workplan may not be achieved. The number of ongoing/to be finalised activities for 2024 appears on first glance relatively high, with some risk of moving tasks to 2025, which may impact completion of newly started initiatives. While the structure of the workplan has been simplified compared to the previous version, it is nevertheless difficult to follow the intended process, as related topics appear in several places, covered by different functions. It could be beneficial to define overarching development needs and then define how those are achieved over the years with respective concept paper and guidance development. The topics defined appear relatively broad. While QSP is named in the tactical goals section, reference to QSP methodology and guidance appear missing in sections 3 and 4. QSP could potentially play a larger role in motivating clinical development program designs, including for the development of peptides, where large amount of data on MoA might already be available for mABs. In addition, combination drug development might benefit from insights generated through QSP. It would be helpful to lay out specific guidance on how QSP could increase efficiency in study designs and what requirements would need to be fulfilled for validating underlying modelling assumptions. The wide topic of Estimands has been named in section 2 but is spelled out in sections 3 and 4 only for the meta-analysis problem. At the ACT-EU workshop in November, emphasis has been put on issues of treatment switching in Oncology studies. While switch of therapy may not be desired by design, it will likely continue to be implemented in practice and will impact estimation of Overall Survival in Oncology Clinical Trial. As such, this topic, or a broader topic on decision making beyond randomization (as discussed at the ACT EU workshop) may be of relevance for consideration in the workplan.
		Workplan is ambitious covering many relevant areas. Some areas are noted as being cross functional in ability to complete. Would be useful to highlight which working groups will be

2	EFPIA	involved in the various tasks and clarify how to ensure the appropriate M&S working group members are engaged to provide input as part of scientific advice.
3	EFPIA	It is hard to get the vision and strategy from the bullet point list of goals. The elements are presented as being independent of each other, but many are interconnect, and some are operating at a higher level. For example, credibility assessment framework (line 221) is mentioned quite late in the document flow as under multidisciplinary. The fact that this is an overarching process for M&S and maybe AI/ML is a bit lost. Similarly, how the proposal for “Concept Paper on the use of the credibility matrix framework for decision making “ will operate vs the ICH guideline that is under development is not clear. A concern would be that the EMA will end up with conflicting regional guidance. Similarly, related areas that are mentioned in the ‘activities’ sections, but not in the M&S Tactical Goals, is the contribution of M&S to: • pregnancy and lactation guideline • clinical pharmacology for oligonucleotides and peptides The important role of M&S for DDIs is not mentioned tactically, nor is the important role of simulations for clinical trial design. A proposal is that having an introductory section laying out the overall strategy with perhaps a diagram/table showing how these guidelines inter-relate would be more useful for industry to understand . Similarly having clear statements in the various areas re the EMA strategy for regional vs ICH level guideline development would help enormously.
4	EFPIA	How will general evidence standards be set in the future, in particular the need for guidance on how mixed evidence sources should be presented for evaluation?

5	EFPIA	We recommend that the MWP provides additional guidance o on when would novel endpoints be acceptable for regulatory decision making (e.g., biomarker based like ctDNA - circulating tumor DNA), or MRD (Minimal Residual Disease) in oncology indications; or imaging based, digital endpoints, etc.…). This topic could fit into some of the existing activities laid out in Section 2.1 and cover issues around surrogacy, but also the acceptability of composite endpoints, non-standard endpoints, novel technology or machine learning based endpoints. This could also include settings where novel parameters /endpoints are already used for clinical decision making and patient management, but where these are not yet acceptable from a regulatory perspective.
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		

2. Specific comments on content of the Workplan

Section 1. Strategic Goals

Please include your comments on the long term and short term strategic goals.

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	36-38	EFPIA	Helpful if the EMA could release guidance on topics on what the FDA has recently launched such that applicants can assess the potential alignment between regions, e. g., Guidance on paediatric IBD, RWE guidance, etc.	Add a statement to reflect there will be collaboration where possible with other regulatory agencies for potential to align between regions.
2	45-46	EFPIA	While the credibility concepts for MIDD are appropriately mentioned in the 'activities' sections in several places, they are not mentioned clearly in the earlier strategic or tactical sections. Specifically, the concept of credible models being used to provide evidence to support decisions is not clearly made in the strategic goals. Making well informed model-based decisions is the 'why' of the methodology we are discussing. Credibility of models for decision making should reach up into the strategic goals.	Extend the statement as follows: "Strive for methodological excellence across the EU Network to ensure best methodological practice in assessment and advice procedures" to produce credible model-based evidence that supports development and regulatory decisions.
				- Data Quality and Integrity: Ensuring the accuracy, consistency, and reliability of data used by AI systems is crucial. Poor data quality can lead to incorrect conclusions and affect trial outcomes. - Patient Privacy and Data Security:

3	102-111 Data Science & AI	EFPIA	Several key considerations to be kept in mind should be highlighted, to lead to more efficient and reliable outcomes in clinical trials.	Protecting patient information is paramount. AI systems must comply with data protection regulations like GDPR and Health Insurance Portability and Accountability Act (HIPAA) to safeguard sensitive data. - Ethical Considerations: Ethical issues such as informed consent, transparency in AI decision-making, and avoiding biases in AI algorithms need to be addressed to maintain trust and fairness. - Regulatory Compliance: AI applications in clinical trials must adhere to regulatory guidelines set by authorities like the FDA and EMA. This includes validation and documentation of AI tools to ensure they meet regulatory standards. - Interdisciplinary Collaboration: Successful implementation of AI requires collaboration between data scientists, clinicians, and regulatory experts to ensure that AI tools are effectively integrated into the clinical trial process. - Continuous Monitoring and Validation: AI systems should be continuously monitored and validated to ensure they perform as expected and adapt to new data and conditions.
4				
5				
6				
7				
8				

9				
10				

Section 2. Tactical Goals

Section 2.1. Guidance activities

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	57	EFPIA	In addition to those complicated formulations, a topic of relevance could be combination products. Increased understanding of mechanistic pathways and development of novel drugs on common pathways may also motivate development of novel combination drugs for which information on additive or synergistic effects may already be available.	Include into the list of examples “drug combination“.
2	62-71	EFPIA	Further guidance to the applicant based on experience from M&S working party would be appreciated for paediatric field where extrapolation and M&S is key in the paediatric drug development.	Add to last sentence alignment with ICH E11A
3	68	EFPIA	Spelling out of QSP is missing in sections 3 and 4. QSP is most likely covered through multiple work items in sections 3 and 4, still it would be good to spell out more specifically, which guidances or concept papers will inform QSP guidance.	Update sections 3 and 4 to reflect where QSP will be covered.
			We welcome the plans to update the language and concepts in many EU guidelines in view of the ICH E9(r1) guideline (line 73-77). The estimand	

4	73-77	EFPIA	framework is very closely related to causal inference and we would encourage embedding language and concepts associated with causal inference in the guidances as well.	Add reference to increasing use of causal inference methods following ICH E9(R1).
5	87-101	EFPIA	We appreciate these efforts. The increased use of high-dimensional data across the context of use of biomarkers will be expected to contribute fundamentally to drug development, for example by increasing mechanistic and patient-level understanding of variation in efficacy, safety, and other aspects of the disease-drug interaction. This may also broadly influence trial designs directly, beyond companion diagnostics.	Additional guidance on these aspects will be welcome.
6	106-112	EFPIA	We recommend that the MWP commit to issuing a framework that outlines the regulators' general approach to risk assessment. This will aid the entire field and could be generated quickly based on exiting frameworks and are more suitable for a topic like AI which requires an agile regulatory approach.	Refer to guidance on key principles and framework underpinning AI/ML use cases.
7	112-119	EFPIA	Consideration should also be given to the development with relevant stakeholders on fit for purpose RWE methodologies and analytical approaches for regulatory decision making in general.	Add reference to 'fit-for-purpose' RWE methodologies and analytical approaches.

8	129	EFPIA	It is unclear if this is proposed in response to/linked to ICH M15.	Add ‘and ensure consistency with ICH M15’
9	132	EFPIA	Reflecting the mentioning of the release of the Bayesian Concept paper for 2024 it is considered of key importance to prioritise.	Confirm Bayesian Concept Paper will be prioritised.
10	138	EFPIA	A platform trial reflection paper for paediatrics and oncology would be highly appreciated as well as the Guideline on predictive biomarker assay development.	
11	151	EFPIA	This is a broad statement, so it is suggested that the types of topics to be covered be specified e.g. model validation, verification, context of use etc. Clarification is requested regarding whether this includes PBPK and PBBM.	Add some more detail to the sentence including which groups/WPs could be involved
12	172	EFPIA	ICH M13A refers to the use of M&S in sections 2.1.5 and 3.4. Clarification is requested regarding this will be complementary to that guidance (also as well as to the guidance in ICH M13B and C when available.	Suggest clarifying in text
13	175	EFPIA	Revision of Adaptive design to take into account outputs of ICH E20: - invite the MWP to consider on conditions to use adaptive design within a pivotal trial and potential impact on Guideline on clinical evaluation of anticancer medicine products (EMA/CHMP/205/95 Rev.6” – currently	Refer to ‘ICH E20 and other guidance’

			trials with adaptive design are limited to address “non-complex” (dose) questions and rather not acceptable for marketing authorization	
14	182	EFPIA	While dose-finding is certainly a relevant application of Modelling & Simulation, this topic may better be placed in the multi-disciplinary work items to clearly indicate that the importance of Biostatistics input, as well its relevance to Statisticians for Design and Analysis considerations in Is future clinical trials.	Move this topic to multi-disciplinary
15	194	EFPIA	To acknowledge the evolving clinical research landscape, and to facilitate proposals utilizing tools such as Bayesian methods this topic is considered of priority. Whereas the current workplan May 2022-Dec 2024 mentions EMA workshop on CP / RP on Bayesian statistics (Q3 2024) and whereas this activity is not yet announced by EMA (as of Aug 2024), it is highly relevant that the proposed draft workplan 2025-2027 takes account of this workshop, especially and in particular relevance in context to the listed anticipated release of Bayesian Concept Paper as listed for 2024.	Add a Stakeholder workshop on Bayesian statistics
16				
17				
18				
19				

20				
21				
22				
23				
24				
25				
26				
27				
28				
29				
30				

Section 2.2. Training and workshop activities

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	194	EFPIA	While the Bayesian guideline is expected only in a couple of years, it may be good to have some initial training activities planned already based on the concept paper. Some previous surveys have indicated that the biggest barrier for use of Bayesian methodology in industry and acceptance by the regulators is due to lack of skills to interpret such results (Ruberg et al, 2023) Application of Bayesian approaches in drug development: starting a virtuous cycle - PMC (nih.gov); https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9931171/	Add Training on interpretation of Bayesian statistics
2	195-202	EFPIA	It is recommended that approximate timing be added for the workshops.	Add to text
3				
4				
5				
6				
7				
8				
9				
10				

Section 2.3. Communication and stakeholder activities

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				

Section 2.4. Multi-disciplinary collaboration

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1		EFPIA	Consider collaborations with the Inspectors Working Group. We note they have hosted two workshops on AI in the past and sponsors need clarity on the expectations for inspections of activities along the drug development lifecycle.	
2	211	EFPIA	This could be achieved via multistakeholder workshop including consortia and learned societies in which selected case studies that illustrate the conceptual approach are presented.	Add reference to raising understanding of methodological aspects involved in establishing novel biomarker or endpoints, specifically intermediate or surrogate endpoints
3				
4				
5				
6				
7				
8				
9				
10				

Section 3. Operational Goals

Please include your comments on pre-submission activities, evaluation and supervision activities.

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				

Thank you

Thank you for your contribution.

Contact

Contact Form