Draft revised consolidated 3-year work plan for the Methodology Working Party (MWP)

1. General comments

	Stakeholder name (*to be repeated in all rows*)	General comment
1	EFPIA	Regarding the RWE section: Can you clarify how these priorities are connected with other RWE initiatives/guidance? For example, the EMA RWE guidance on registry studies, IHI proposed topic "Development of practical guidance and recommendations for using real world data/real world evidence in healthcare decision-making". Consider other priorities given there is increasing focus on RWE methodology and analytics, for example: 1) Overview of RWE methodological advancement and case studies; 2) Enhance Methodology Working Party collaboration with other EMA NCA RWE groups methodological tools/systems such as DARWIN EU Standardised Analytics to enhance the methodological alignment for RWE?
2	EFPIA	We welcome EMA's draft revised Methodology Workplan and would encourage EMA to include a more granular timeline similar to the approach taken in the Big Data Steering Group Workplan and AC EU Workplan.
3	EFPIA	Regarding clinical trial modernisation and use of estimands: 1. The following biostatistics guidelines are proposed to be updated in relation to ICH E9(R1): a. Guideline on adjustment for baseline covariates in clinical trials: We welcome an updated guidance that reflects recent methodological advances, for example methods like as targeted maximum likelihood (TMLE) for robust adjustment of prognostic baseline covariates. It would also be of value to develop guidance

		on reporting marginal causal effects in line with usual target estimands. b. Points to consider on application with 1. meta-analyses; 2. one pivotal study: We would welcome an updated guidance that integrates the estimand framework and how to align estimand attributes across different trials in the context of a meta-analysis. c. Reflection Paper on Methodological Issues in Confirmatory Clinical Trials Planned with an Adaptive Design: When the finalization of ICH E20, currently planned for Q4 2025, is achieved, we would welcome a guidance that reflects new developments within the area (for example enrichment designs) and reporting of adaptive trials in general. 2. An update is welcome of the clinical pharmacology guidance on bioequivalence, Guideline on the Investigation of Bioequivalence, with considerations on implementation of the estimand framework to ensure a clear upfront agreement on under which conditions, bioequivalence should be established. This is particularly important for drugs where bioequivalence cannot be established by single dose and where a crossover design is not possible. 3. The RWE guidance would benefit from being updated to reflect the need for estimand considerations in study protocols for non-interventional studies that are used as supportive evidence in MAAs. This will clarify what the estimated treatment effect entails and facilitate the link to the clinical trial results. A clear guidance on use of RWE for regulatory submissions including considerations for product labels is needed. Aspects to cover include: which data is applicable, which analyses are preferred and for which outcomes, which framework to use e.g. Estimand, or PICO or HARPER etc. 4. For the reflection paper on the use of single arm trials further guidance on when synthetic controls can be used to support regulatory decision making.

		5. In the section on data science and AI a link/reference to RWE is missing as the data science/AI work often relies on RWE data. 6. A new guideline on the design, analysis and reporting of outcome trials is welcomed. This should also describe (general) considerations on the estimand(s), including relation to censoring, guidance on population summaries, and reflections on treatment conditions.
4	EFPIA	We encourage the Methodology Working Party to consider the following topics: • Accelerated pathways for co-development of SaMD alongside pharmaceutical trials; • Digital/ML-derived endpoints; • Validation of surrogate biomarkers to approximate multimodal composite markers (i.e., scalable proxy measures in lab tests or imaging modalities that approximate more expensive/less scalable measurements); • Enriched trial designs (model-based and/or RWE) - potentially allowing reducing trial sizes and/or durations.

(Add more rows as needed)

2. Specific comments on text

	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	45-63	EFPIA	The Strategic goals of the Workplan could mention the general context around supporting innovation and the acceleration of clinical development (i.e., ACT-EU).	Add under 'Strategic goals': • 'To support ACT-EU's mission to strengthen the EU as a region that supports clinical trial development and enables collaboration and innovation.'
2	71-72	EFPIA	Unclear how to interpret "controversial".	Remove 'and controversial ones'
3	73	EFPIA	It is recommended that the list of example complex formulations be extended to include combination drug-device products.	Increasing complexity is encountered when abridged applications are made to increasingly complicated formulations **and products**, e. g., long acting injectables, locally acting agents, biologicals (biosimilars), **combination drug-device products.**
4	73, 100	EFPIA	We would recommend including changes in cell line during development for biologics as a potential topic for guidance, especially when non-clinical and clinical evaluations are needed. Guidance is currently limited, with a stronger focus on biosimilars.	'Increasing complexity is encountered when abridged applications are made to increasingly complicated formulations, e.g., **changes in cell line during development for biologics,** long acting injectables, locally acting agents, biologicals (biosimilars), possibility of making

				synthetic copies of biological drugs, etc.' Add under 'Long-term': • **'Guidance on changes in cell line during development for biologics'**
5	78	EFPIA	We would recommend including examples for newer treatment modalities.	'Clinical pharmacology expectations for many of the newer treatment modalities **(e.g., Car-T, ADCs, etc...)** are not covered by current EMA guidelines…'
6	86	EFPIA	For consistency with line 82, suggest referring also to peptide related reflection paper although it is unclear under the appropriate section (short or long term)	
7	101	EFPIA	We would recommend including long-term guidance on immunogenicity and SMPC labelling of immunogenicity data, information, and implications. The FDA has recently prepared and released such a guidance.	Add under 'Long-term': • '**Guidance on immunogenicity and SMPC labelling of immunogenicity data, information, and implications**'
8	111, 124	EFPIA	Clarification is requested as to whether discussion of Physiologically Based Biopharmaceutics is also to be addressed in this section.	
9	123	EFPIA	We would recommend including mechanistic models and Tumour	'Concept Paper and/or Q&A on design, conduct, qualification and

			Growth Dynamic models as examples.	reporting and use of exposure response models (including QSP, **mechanistic models, Tumour Growth Dynamic**) in regulatory submissions.'
10	129	EFPIA	We would recommend including potential guidance on Posology updates to SMPC using MIDD approaches, especially given precedence for PD-1/PDL-1 compounds.	Add under 'Long-term': • '**Guidance on Posology updates to SmPC using MIDD approaches**'
11	141-142 & 352	EFPIA	The use of RWD in the context of clinical trials e.g., considerations of trial designs that prospectively include external control data, is mentioned as an example of future topics considered by the BWP, while this is not reflected in the priorities of the Working Party. There should be specific priorities planned for the use of external control data in clinical trial design and conduct.	
12	142, 145, 147	EFPIA	It would be beneficial if the guidance could also address the relationship between the RWE generated by industry and RWE generated by DARWIN EU to support EMA's decision-making, especially in the context of clinical trial design considerations.	

13	148 – 2.1.3 Section	EFPIA	A proposal reflection paper or guidance document on dose finding studies in general (like the recent one by FDA: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/optimizing-dosage-human-prescription-drugs-and-biological-products-treatment-oncologic-diseases) may be useful rather than a specific one for pharmacometrics.	Add under 'high priority/short-term': • Reflection paper on dose-finding studies
14	163 & 167	EFPIA	Use of external data is currently mentioned in RWD, but it also highly relevant to other planned reflection papers/guidance documents such as single arm trials and Bayesian methods.	• Reflection Paper on the use of single arm trials**, including recommendations on the use of external data**. • Reflection Paper on Bayesian methods in clinical development**, including recommendations on the use of external data**.
15	163 & 358	EFPIA	The draft Reflection Paper on the use of single arm trials was already released; should this reflect finalising it?	'**Finalising the** Reflection Paper on the use of single arm trials'
16	166	EFPIA	The position paper on master protocol is relevant as we see more and more studies that are utilizing basket/umbrella designs. The link below on the FDA guidance document on Master Protocols:	

			Efficient Clinical Trial design Strategies to Expedite Development of Oncology Drugs and Biologics Guidance for Industry (March 2022) could be relevant. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/master-protocols-efficient-clinical-trial-design-strategies-expedite-development-oncology-drugs-and There is a need for regulatory guidance for use of master protocol and to understand the issues such as use of the right type of control, different types of biases such as temporal bias if some of the control subjects were collected much earlier in the study; operational bias is also challenging as it is important to maintain data integrity, etc.	
17	167	EFPIA	The proposal to develop a guidance document on use of Bayesian methodology in clinical trials is a great step forward. The following FDA guidance document (February 2010), for medical device trials could be useful: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-use-bayesian-	

			statistics-medical-device-clinical-trials We agree that regulatory guidance documents are needed to ensure the required evidentiary standards and to facilitate their performance evaluations, especially since the frequentist concepts such as alpha-spending function and type-I error control are not well understood in the Bayesian framework.	
18	167	EFPIA	It is proposed that a framework for validation of digital endpoints framework also be considered for development.	Reflection Paper on Bayesian methods in clinical development. **Framework for validation of digital endpoints framework**
19	189	EFPIA	It is recommended that consideration be given to addressing also guidelines related to use of patient reported outcomes and surrogate end-point validation	Revision of Good Pharmacogenomic Practice (EMA/CHMP/718998/2016). **Guideline on the use of patient reported outcomes. Guideline on surrogate end-point validation is also addressed.**
20	190-199	EFPIA	With respect to use of AI in pharmacovigilance, we support the development of a guideline with the following recommendations: • A clear definition of AI will be particularly important for PV and 'medium/high risk' applications, as there	

			may subsequently be a need to differentiate between narrow AI usage e.g. a regression model from wider AI e.g. use of LLMs e.g. as chatGPT. • Validation capabilities exist within PV organisations for software and automations. These existing capabilities enable a trusted environment today. We believe these capabilities can be leveraged to validate AI/ML in production. • We would discourage the MWP from reviewing "lines of code". Reviewing AI/ML algorithms in detail is contradictory to current thinking about software and automations. • Quality Management Systems will be essential and key for ensuring trusted use of 'black box' AI where access to all training data and all code is infeasible. If an	

			organisation has appropriate controls/process in place to monitor algorithm performance, then getting inside the “black box” will not be necessary. • A clear distinction should be drawn between AI/ML supplementing the job a PV professional performs (i.e. assisting) and AI/ML performing a GxP task independently. • It would be helpful to see alignment between EMA/EU and FDA/US guidelines, e.g. reference the National Institute of Standards and Technology (NIST) risk framework and seek alignment with any future US AI Safety Institute technical guidance. • It will be important to understand how data quality and methodology will be assessed by the Agency to guarantee AI	

			maturity for clinical development.	
21	229	EFPIA	Clarification of whether the term “digitalised SmPC” refers to electronic product information would be welcome.	
22	230	EFPIA	It is proposed that reference to the data quality framework be moved to the relevant sections on RWD (line 147 and 355).	
23	251 & 388	EFPIA	The only workshop planned in relation to trial modernization relates to the Concept Paper on Bayesian statistics. There should be consideration for other workshops related to other aspects of trial modernization as outlined in the Workplan, such as on single arm trials, platform trials or external control data.	Add workshops such as: • ‘EMA workshop on Reflection Paper on the use of single arm trials. • EMA workshop on the Reflection Paper on platform trials. • EMA workshop on external control data’
24	257	EFPIA	We welcome EMA’s workshop on Dose optimization, especially given the FDA Project Optimus initiative on dose optimization in oncology development. We would recommend considering a guidance on dose optimization for oncology and non-oncology compounds.	
25	268-270	EFPIA	We would encourage cluster meetings to also include the US FDA to ensure further alignment of	‘Continue to have cluster meetings in the areas of biostatistics, pharmacometrics,

			regulatory strategies relevant to methodologies between EMA and FDA.	genomics, generics, and RWE. These may also be with **US FDA,** Health Canada, Japanese and Australian regulators, and others depending on the area and interest.'
26	355	EFPIA	Consideration could also be given to developing a framework to reduce uncertainty around proposals for alternative RCT approaches.	
27	453	EFPIA	The timing of workshops may need to be arranged according to the specific needs of the guidance – either before the guidance is finalized to gather views and expertise; or once it is finalized for training purposes.	Add: 'All relevant guidelines developed or revised will need to be supported by a workshop including industry, as appropriate. **The timing of workshops may be arranged according to the specific needs of the guidance – either before the guidance is finalized to gather views and expertise; or once it is finalized for training purposes**.'
28	455-457	EFPIA	It is important to consider multi-stakeholder consortia such as TransCelerate/IMI/IHI and the outcome of their work.	Add: 'For the longer term it will be explored if interactions can be expanded to academic organisations with key roles in the drug development life cycle, professional organisations**, ~~as well as~~** patient representative organisations**, as well as multi-**

				stakeholder consortia such as TransCelerate/IHI.'

(Add more rows as needed)