EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 January 2023

Submission of comments on 'Concept paper on platform trials' (EMA/CHMP/840036/2022)

Comments from:

Name of organisation or individual
EFPIA

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	We recommend that the CHMP drafting team consider the output from the IMI EU-PEARL project that is due to sunset in April 2023. During the EU-PEARL project, there have been numerous discussions with regulators, including the US FDA and the EMA Innovation Task Force. In addition, the EU-PEARL project has held two Stakeholder Workshops that have included participation by EU regulators, ethics' committee representatives and many other stakeholders. All of the issues to be considered as part of the CHMP drafting group have been extensively discussed during these interactions. Thus, rather than trying to 'reinvent the wheel' and duplicate discussions that have already been held, the deliverables from the EU-PEARL project should be taken into consideration when drafting a CHMP document on platform trials.	
	It should be recognized that there is not 'one way' to do platform trials and a certain level of flexibility should remain in the reflection paper to encourage innovative designs adapted to the research being conducted. The field of platform trials is fast-evolving. It will be helpful to provide examples of how the scientific discussions outlined in the reflection paper can be operationalized (e.g., use of DMCs, blinding).	
	It would be helpful if the reflection paper could address how multiple changes may be justified in a platform	

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	trial, i.e., guidance in rationale for several changes, such as prospectively identifying potential key inflection points (Interim Analysis from other arms/external data which may influence changes) and how to avoid bias from these changes. In particular, different interim analyses could be conducted at different time points for different treatments. Guidance on how to firewall these analyses properly, e.g. to avoid the disclosure of the response under control, would be helpful. If the treatments share a similar MoA, an interim on one treatment could also indirectly inform the expected response under other treatments. In a platform trial consisting of treatments sharing a similar MoA compared to the same control arm, could the guidance cover the assessment of the benefit/risk profile of a given treatment would remain uninfluenced by results from other treatment arms?	
	The use of non-concurrent controls is a critical consideration for platform trials where time trends may bring bias and should be addressed. However, there is no mention of potentially using historical controls in the confirmatory platform trial setting which sponsors may adopt in certain situations. Historical and non-concurrent controls share several sources of potential bias, and guidance on how to appropriately utilize historical controls in the platform trial setting is highly desired.	

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	Unlike a traditional multi-arm trial, the platform trials allow the IMPs to be dynamically added in and taken out; and the IMPs may not necessarily be well defined upfront. This feature can make the FWER control very complicated in a platform trial setting. Ideally the draft guidance will include some regulatory perspective on this topic and recommendation on the relevant methodology for the use. For example, some so-called online control of error rate has recently appeared and referenced in the literature (e.g. Tian and Ramdas. "Online control of the familywise error rate." Statistical Methods in Medical Research 30.4 (2021): 976-993; Wason and Robertson. "Controlling type I error rates in multi-arm clinical trials: a case for the false discovery rate." Pharmaceutical statistics 20.1 (2021): 109-116).	
	It would be helpful if separate supportive Q&A/documentation could also address best practices for seamless study transitions (i.e., timings, minimum requirements for adding and deleting arms, flexible controls, etc) in a confirmatory trial.	
	The future reflection paper should address design/analysis elements to be considered when control arm/data are shared in an unblinded manner while the master protocol is still enrolling other active sub-protocols. In addition, the reflection paper should highlight any differences between exploratory and confirmatory settings.	
	The future reflection paper should consider the following regarding Type I Errors:	

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	• If there is no overlap/sharing of data across subprotocols, then the reflection paper should clarify that splitting alpha across indications/subgroups/comorbidities is not required (similar to traditional development in multiple independent studies). • Address additional/different considerations (if any) in single sponsor vs. multi-sponsor master protocols.	
	Howard et al (Howard, Dena R., et al. "Recommendations on multiple testing adjustment in multi-arm trials with a shared control group." Statistical methods in medical research 27.5 (2018): 1513-1530.) introduced the notion of probability of multiple superior false positives hypotheses in case of a random low under placebo. This is sometimes used in various conferences and workshops as a justification for reducing the local alpha used for each treatment (assuming a random low would be unlikely to occur in several independent trials). It would be useful to know if and when this really is of concern. Indeed, adjusting this error to the same level as the one encountered in several trials would require a local alpha which is even smaller than the one obtained with the aggressive Bonferroni correction (i.e. controlling the FWER does not control the probability of MSFP). This would seem like an overkill for a phenomenon that would be hard to detect, and not more likely than a random high on placebo.	

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	A discussion on how to frame the estimands relative to different treatments in the platform trial would be helpful. Another issue is the potential change of the control arm over time. The trialist will need to reflect if the original estimand can still be estimated or if it needs to be updated because of the unplanned change of control. Alternatively, this could be foreseen at the planning stage and the original estimand could be aspecific and simply mention that the experimental treatment is compared with a state-of-the-art control therapy. A discussion covering these points would be helpful. Please see: Collignon, O., Schiel, A., Burman, C. F., Rufibach, K., Posch, M., & Bretz, F. (2022). Estimands and Complex Innovative Designs. Clinical Pharmacology & Therapeutics.	

Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
6		Comment: The inclusion of "Master Protocols" in the list of key words may raise questions about whether this guidance is applicable to Basket and Umbrella Studies Proposed change (if any): Clarification of the scope	
16-40 (problem statement) & 41-50 (discussion)		Comment: Operational & transparency aspects covered in other guidelines (such as the Complex Clinical Trials Q&A) will need to be updated in line with the conceptual thinking of platform trials that will be described in the reflection paper. Unique impacts on operational aspects of the ongoing confirmatory platform trials: e.g., disclose part of trial data (group-level summary of completed arms and the corresponding controls) on CT.gov; agencies post their review documents to public (completed arms for drug approval); approved drug label. Proposed change (if any):	
19-22		Comment: It would be helpful if the reflection paper also discussed scenarios /methodological aspects in relation to platform trials conducted early in development (e.g. signal seeking) for the generation of data for subsequent trials and to support conditional MAA vs the use in confirmatory trials. Proposed change (if any):	

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21		Comment: Efforts have already gone in developing protocol templates to support platform trials (e.g., IMI EU-PEARL) – it would be beneficial to include a reference to this protocol template/tools in the reflection paper to understand the kind of designs which could be acceptable. Proposed change (if any):	
24		Consider expanding the list of complexities of platform trials to include informed consent (e.g., complexity of information for the ICF; consent before/after randomization).	
Lines 25-26		**Comment:** Clarity on "requirement for Type I error control at the level of a platform trial …" is needed: the current language indicates that Type I error control is required for confirmatory trials but in the presence of multiple hypotheses, it is important to evaluate if the hypotheses are inferentially independent or not (e.g., the case of "different drugs with different mechanisms of actions" is quite different from the case of "different doses of one drug"). The guidance may first provide the "context" where multiplicity control is genuinely needed or unadjusted analyses should suffice, and then introduce the methodologies for (strong) control of Type I error. The document would also probably need to acknowledge the existence of a grey zone: academic trials such as RECOVERY tested several repurposed drugs against COVID19 in a single platform. These comparisons were not adjusted for multiple testing, although one could argue that the finding of "at	

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		least" one efficient drug in that setting would have been a success. In relation to this, a discussion on how to define the actual family of hypotheses to be tested would be welcome. One could indeed argue that, although being tested within the same platform trial, hypotheses that would eventually support the assessment of the benefit/risk profile of very distinct medicines would belong to different sets of family (each of them being then granted 5% of FWER), in opposition to a case of several doses of the same treatment which would give several chances of claiming success for the very same medicine. A discussion on the notion and degree of independence between the hypotheses and how it relates to the need of adjustment would also be helpful. For example, these scenarios of platform trials show different degrees of dependency between the hypotheses while each of them support different treatments: • Several sub-studies governed by the same protocol, each of them comparing a different treatment vs its own control • One single RCT with different treatments vs one single control • One single RCT with different treatments vs one single control but a hierarchical model is used to leverage the treatment effect across arms (e.g. because they have the same MoA)	

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		Proposed change (if any):	
32		Comment: please consider adding the follow questions for CHMP position: • Evaluation of the scale of the confirmatory platform trials (e.g. the maximum number of allowed active arms, total duration of the platform trial, open-ended or not) on the operating characteristics and bias. • Proposed change (if any):	
35-38		Comment: Non-concurrent control may in certain cases be a pragmatic approach for platform trials. We would suggest adding in the reflection paper guidance or requirements for the sponsor to address the statistical caveats. It would be helpful to have clarity on the acceptable use of non-concurrent controls (i.e., limited number of concurrent controls, consistent treatment effect observed between concurrent, non-concurrent & historical /observational data to support reliability of the concurrent data for comparator use). Some guidance on how to pre-specify and deal with an analysis involving non-concurrent control would be welcome. For example, doing so would likely require a model accounting for time trends, and only if this model is accurate and consistent over treatment arms, the Type I error will be protected. Guidance on how to justify this model and how to present the different operating characteristic would be important.	

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		In addition, recommendation on the types of supplementary /sensitivity analyses needed, e.g. with and without non-concurrent control, would be helpful. Proposed change (if any):	
38		Comment: The concept paper does not discuss the use of platform trials in the context of paediatric drug development when some degree of extrapolation is appropriate. The use of extrapolation (i.e. borrowing data from an appropriate reference, usually adult, population) could elevate the Type 1 error (as discussed in ICH E11A). As such, a discussion of the use of a platform trial in this context would be useful, as one will be unable to generalize from the comments in a non-extrapolation context. In addition, it would be helpful if the reflection paper could discuss, how, in the framework of paediatric drug development, platform trials would be justified in support of paediatric indications and what would be the methodological aspects and how external comparison could be done. Proposed change (if any): … it 38 will be discussed whether this can be reasonable. **Other considerations include the impact of extrapolation (i.e. borrowing data from an appropriate reference, usually adult, population) on elevating the Type 1 error (as discussed in ICH E11A).**	
39-40		Comment: While there may be certain settings that lend themselves to platform trials (i.e., biomarker restricted population, high unmet need, rare population), it would be	

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		helpful to recognize that there may be unique circumstances that have not yet been applied to platform trials. Proposed change (if any):	
43		Comment: Such concepts should be aligned/ drawn keeping in mind terminology as defined by other regulators globally to avoid inconsistencies. In instances where terminology differs, this should be clearly outlined and explained. Proposed change (if any):	
46		Comment: To complement the CTFG Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials (2019) it is suggested that the concept paper refers to appropriate documentation of platform trials in clinical trial protocols. Proposed change (if any): • CHMP´s position on increased complexity and uncertainty in decision making related to confirmatory platform trials. • **Use of platform trial in the context of paediatric extrapolation.** • **Documentation of platform trials in clinical trial protocols.** ~~The last topic~~ **Topic 3** will be divided into subtopics related to:	

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53		Comment: Suggestion to include also the benefits of platform trials and not only the issues Proposed change (if any): '…account the **benefits and** issues…'	
56 & 64		Comment: The terms 'guideline' and 'reflection paper' are used interchangeably throughout the concept paper. Could it be clarified that the timelines outlined in this concept paper relate to the drafting of a reflection paper, and not to the drafting of a guideline with a reflection paper as an intermediary step? Furthermore, it is proposed to conduct two workshops: one before drafting the reflection paper and one after the consultation period is over. Proposed change (if any): 'proposed date for release of draft ~~guideline~~ reflection paper 03/2024'; ~~'A~~ workshops with external stakeholders at the start and end of the ~~guideline~~ reflection paper writing process will be essential.'	
76-77		Comment: We encourage the Agency to exchange with other regulators globally to ensure the reflection paper is aligned with other key guidances. Exchanging best practices amongst health authorities globally is important to ensure a successful global approach to platform trials' development. Proposed change (if any):	

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78-85		Comment: A reference should be added to the ICH E20 Concept Paper on Adaptive Clinical Trials, in view of the impactful work which will be completed by the Expert Working Group in the next few years. Proposed change (if any): Addition: 'ICH Final Concept Paper E20: Adaptive Clinical Trials, dated 7 November 2019'	

Please add more rows if needed.