28 May 2024

Concept paper for the Development of a Guideline on Non-Inferiority and Equivalence Comparisons in Clinical Trials – EMA/65012/2024

1. General comments

	Stakeholder name (*to be repeated in all rows*)	General comment
1	EFPIA	The title of the concept paper appears to focus on comparisons in clinical trials to answer non-inferiority and equivalence objectives. Indeed, a clinical trial objective could include superiority and non-inferiority objectives. However, the text of the concept paper refers to non-inferiority trials. It might be beneficial to embed guidance on how to answer non-inferiority research questions in a global guidance such as ICH E9 (as appendix)?
2	EFPIA	We recommend that the Agency includes in the Concept Paper recommendations for establishing non-inferiority relative to clinical outcomes when leveraging real world evidence.
3	EFPIA	The final guidance should clarify if two estimands are to be specified for the same endpoint (similar to current EMA guidance that requires similar conclusions in analysis from two different analysis sets) and if so, why a single analysis that is sensitive to detect differences is not sufficient.
4	EFPIA	In Section 7, the concept paper states that the new guideline "will improve planning of confirmatory trials that include non-inferiority comparisons and therapeutic equivalence comparisons by sponsors". This seems to imply that the new guideline will only apply to confirmatory trials. If there are trials that include non-inferiority comparisons or therapeutic equivalence comparisons that are out of scope of the new guidance, we suggest to explicitly specify this within the scope of the

		guidance and also provide a discussion why the guidance does not apply to these trials.

(Add more rows as needed)

2. Specific comments on text

2.1. Introduction

	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	none			
2				

(Add more rows as needed)

2.2 Problem statement

	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	44-45	EFPIA	Clinical trials should clearly define what effect the researchers are trying to measure. A single estimand per endpoint that is sensitive to detect differences should be sufficient and ensures that the design of the trial, the way data is analyzed, and the overall interpretation of the results are all aligned with a specific goal.	… constructing a single endpoint-specific estimand that targets a treatment effect that prioritizes sensitivity to detect differences,…
2	46	EFPIA	Recommend agency to address challenged when using more conservative statistical analyses.	For example, re-evaluating the need for time consuming approaches that may slow down development of research and prolong access for patients.
	Lines 51-56 (regarding the four objectives)	EFPIA	The list of objectives is useful and acknowledges there are more than one consideration to designing a non-inferiority study. The following suggest an	

			additional objective and some re-wording of one of the listed objectives: 1) An important additional objective may also be related to latency of the outcome relative to a surrogate primary outcome powering the trial (e.g., non-inferiority on survival outcome in a long-latency cancer when progression was the primary outcome; non-inferiority on MACE when Hba1c was the primary outcome). That is, the objective of the non-inferiority is to make trials feasible with the expectations that a longer duration of follow-up or a large study could potentially demonstrate benefit. Consider adding this objective in your list 2) The phrasing of objective (3) is unclear. Consider rephrasing to “Rule out	

			an excess risk compared to standard of care therapy"	
3	51 - 56	EFPIA	Problem statement should consider also comparisons to external controls and comparisons using PROs e.g., when the objective is to demonstrate superiority in overall survival but maintaining HRQoL (non-inferior PROMs) for example when evaluating combination therapies in oncology.	
3				

(Add more rows as needed)

2.3 Discussion (on the problem statement)

	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	60 - 70	EFPIA	Discussion section: the concept should consider also the selection of the comparator	
2	60 - 70	EFPIA	Discussion section: In addition, the concept should include the number of studies needed for a non-inferiority claim and also provide some methodological guidance on evidence synthesis e.g., when 2 non inferiority studies or more will be used for the effectiveness claim.	
3	61	EFPIA	It would be helpful, if the guidance could discuss, in which situations a single trial for non-inferiority may be sufficient for approval.	Add bullet: Guidance on when a single trial for non-inferiority may be applicable.
4	61	EFPIA	Recommend the Paper provides potential alternatives to NI trials when NI studies are not feasible.	
5	61	EFPIA	Recommend agency address blinding issues of NI trials.	
6	Lines 61-63	EFPIA	The discussion of estimands should be tied to the discussion of objectives of non-inferiority and equivalence trials. In line with ICH E9(R1), the discussion of trial objectives and estimands should be clearly separated	• The different types, objectives, and estimands of non-inferiority and equivalence trials, including a discussion on whether estimands should differ in trials

			from trial conduct issues such as trial quality.	with a superiority and non-inferiority objective; • Trial quality and assay sensitivity; Please delete: Estimands, including specific issues relevant to non-inferiority and equivalence comparisons;
7	61, 69-70	EFPIA	Adaptive elements are frequently discussed for non-inferiority and equivalence studies, including blinded sample size-re-estimation. Also switching between non-inferiority and superiority (line 69) and trials including non-inferiority and superiority comparisons (line 70) may include adaptive elements. Examples include the sample size increase for change of hypothesis to superiority, and the termination of enrollment to a “placebo” arm in a three-armed design, if superiority has been established vs. placebo. From this perspective, it will be helpful, if the guidance would include recommendations on	Add bullet: Guidance on adaptive elements in study designs for assessing non-inferiority and equivalence.

			adaptive design in non-inferiority and equivalence settings.	
8	61-62	EFPIA	Recommendation to provide guidance on when inclusion of a placebo arm in an NI trial would be helpful or justified.	
9	62	EFPIA	Recommendation to the Agency to address the potential issues of bias of NI trials where missing data is non-negligible for inferiority null hypotheses.	
10	63	EFPIA	Please also comment on intercurrent event handling strategies for non-inferiority and equivalence comparisons and include case study examples where possible	Estimands, including specific issues relevant to non-inferiority and equivalence comparisons**,** **"**recommendations regarding intercurrent event handling strategies as well as general examples"
11	64	EFPIA	The guidance should provide sufficient detail to clarify the considerations on the requirement to establish non-inferiority in safety, as referred to in line 54 of the concept paper.	Justification of the non-inferiority margin for the different objectives (e.g. establishment of non-inferiority in safety) including difficulties to define the margin
12	64-65	EFPIA	Recommend Agency addresses the importance of both clinical and statistical justification on	

			the determination of NIM. Provide examples of how to justify clinical relevance, especially for endpoints that do not have well-established NIM industry standard (e.g. weight loss).	
13	64-65	EFPIA	The non-inferiority margin is specific to the estimand. For example, the effect of a reference treatment versus placebo generally depends on the intercurrent event strategy, i.e., the magnitude and interpretation of the effect size changes with the intercurrent event strategy. Therefore, a new guidance should discuss how the estimand needs to be considered when determining the margin. Additionally, guidance should be provided on whether historical studies with an unclear estimand or an estimand that is different from the estimand of the current study provide value when determining the margin.	• Justification of the non-inferiority margin for the different objectives including how the margin may be specific to the estimand strategies and the value of studies with an unclear estimand or a different estimand for determining the margin Please delete: difficulties to define the margin;
14	64-65	EFPIA	Recommend Agency to clarify any specific considerations	

			related to safety objectives and analyses in NI trials.	
15	66	EFPIA	Approaches for demonstrating non-inferiority should also be discussed (e.g., 95-95 CI approach with non-inferiority margin or effect size retention).	Statistical analysis, including “methods for hypothesis testing”, analysis sets, treatment of missing data related to the estimand(s), and sensitivity analysis
16	66-67	EFPIA	Non-adherence to treatment should be taken into account in the guidance on non-inferiority trials, so that data can be collected and interpreted in context in order to give accurate reflection overall on whether the drug is non-inferior or not.	Statistical analysis, including analysis sets, treatment of missing data related to the estimand(s) “(including missing data to non-adherence to treatment)” and sensitivity analysis
17	68	EFPIA	Suggestion to provide information on the interrelationship between the topics of "Switching between non-inferiority and superiority comparisons" and "Trials including non-inferiority and superiority comparisons in the statistical testing procedure".	
18	68	EFPIA	Recommend providing guidance on the use on non-inferiority p-	

			values as part of a scheme for controlling multiplicity.	
19	69	EFPIA	Choosing two different estimands for the non-inferiority and superiority objective of a single trial could have implications on the analysis as different statistical estimation approaches are likely to be employed as well as on the communication of results. This should be discussed accordingly in a new guidance.	Switching between non-inferiority and superiority comparisons, including the implication of potentially different estimands and analysis on the communication of trial results.
20	69-70	EFPIA	Recommend Agency to clarify if sponsor can prespecify switching to non-inferiority in the protocol to avoid justifying NIM after unblinding and if the switching endpoint can be considered as one endpoint in the graphical testing strategy.	

(Add more rows as needed)

2.4 Recommendation

	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	none			
2				

(Add more rows as needed)

2.5 Proposed timetable

	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	none			
2				

(Add more rows as needed)

2.6 Resource requirements for preparation

	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	79	EFPIA	Only clinical experts are mentioned for the writing team. Statistical inputs are also critical for such guidance document	The core drafting group will be a writing team of six people including clinical "and biostatistical" experts.
2	Line 83-84	EFPIA	We recommend that the proposed a multi stakeholder workshop is convened earlier in the drafting process to facilitate multi stakeholder	A workshop with external stakeholders (please replace) at the end (with) will be convened as part of the draft guideline writing process is considered.
3	Lines 83-84	EFPIA	There could be value in engaging with external stakeholders not only during the end of the draft guideline writing process, but also at the start.	
4				

(Add more rows as needed)

2.7 Impact assessment (anticipated)

	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	none			

2				

(Add more rows as needed)

2.8 Interested parties

	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	Line 97	EFPIA	We recommend clarifying that input from international regulatory authorities will be sought ahead of the public consultation.	All of the aforementioned stakeholders “and relevant international partners” will be consulted prior to releasing the draft to the public. Please delete: The Guideline will also benefit from the input of other regulatory agencies (e.g. FDA, PMDA).
2				

(Add more rows as needed)

2.9 References to literature, guidelines, etc

	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	none			
2				

(Add more rows as needed)

Other comments

	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	none			
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