<Date of submission>

Submission of comments on 'Concept paper on the need to revise the “Guideline on the 4 evaluation of anticancer medicinal products in man” in order to provide guidance on the reporting of safety data from clinical trials' (EMA/CHMP/292464/2014)

Comments from:

Name of organisation or individual
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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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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	The plan to revise the “Guideline on the evaluation of anticancer medicinal products in man” with respect to improve the reporting of AEs is strongly supported. We recommend describing the current problems of AE reporting in more detail to give a more clear-cut guidance about the specific issues where the guideline needs improvement. We consider differing follow-up periods between treatment groups (or studies) a specifically important problem, because adverse events frequently cannot be attributed directly and causally to the drug under investigation; this is due to the fact that adverse events are also observed without treatment, are based on the underlying disease or are due to concomitant therapies.	

2. 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)*
35-37		Comment: A difference in treatment length is not only a problem across trials. Differences in treatment length are frequently one of the main problems within a controlled trial, because AE observation often is terminated shortly after end of treatment. As a result the comparison of AE between treatment arms is complicated by different observation periods in the treatment arms within one trial. In cancer trials for example treatment and subsequently AE data collection often is terminated after disease progression (or another competing event). If in a controlled trial there is a difference in time to progression, also AE observation periods will differ. While it is reasonable to stop treatment at progression, AEs data collection should be continued for the complete follow-up which should be comparable between treatment groups. If endpoints are not monitored over the complete (and comparable) follow-up period, it is not possible to analyse treatment effects adequately and the corresponding results thus do not represent a fair comparison of treatment strategies. Proposed change (if any): Add some sentences that a difference in follow-up periods between treatment arms within a trial is a major problem in assessing safety and that AEs should be monitored over the complete and comparable follow-up period in all treatment arms to enable a fair comparison of treatment groups.	
35-37		Comment: Even if censoring due to a competing event does not lead to different follow-up	

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		times the presence of competing events is still a problem, because the usual Kaplan-Meier method leads to biased estimations of absolute risks. Proposed change (if any): Add the fact that AEs are always subject to competing risks and that neither simple incidence proportions nor Kaplan-Meier estimates of AE occurrence should be used. The application of appropriate survival time methods for competing risks is required.	
35-37		Comment: It is not mentioned that the presence of recurrent events reveals further problems. Proposed change (if any): Add the fact that the use of appropriate survival time methods for recurrent events is required if multiple events in single patients are counted.	
Lines 32-40		Comment: Some of the problems addressed in the Problem statement seem to be less relevant for controlled trials but specifically relevant for single arm trials (e.g. add-on designs). It might be helpful to distinguish between general problems (relevant in both controlled and single arm trials) and problems specifically important for single arm trials. Proposed change (if any): Please describe specific problems resulting from single arm trials.	
Lines 42-43		Comment: Aiming at improving the understanding of a drug's tolerability by addressing AE reporting might result in the misunderstanding, that the problems could be	

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		solved by improved data analysis and reporting. However, part of the problems can only be solved by improved AE data collection. Therefore, data collection should be added for clarification. Proposed change (if any): The aim of this revision is to find ways on how to collect, analyse and report AEs in order to improve the understanding of the toxicity and tolerability of medicinal products.	
43-45		Comment: The use of event rates per 100 patient-years is only justified if the considered survival time distribution is at least approximately exponentially distributed, which is frequently not the case. Proposed change (if any): Add the information when the use of event rates per 100 patient-years requires the assumption of exponential distribution, which is frequently not valid in practice.	
Lines 77-78		Comment: In addition to the interested parties listed in Section 8, EUnetHTA should be considered Proposed change (if any): Include EUnetHTA as interested party.	
		Comment: Proposed change (if any):	

Please add more rows if needed.