Submission of comments on 'Concept paper on the need for a Reflection Paper on assessment of cardiovascular safety of oncology medicinal products'

Fields marked with * are mandatory.

* Name of organisation or individual

EFPIA

* Country of organisation or individual

Belgium

* Email

katarina.nedog@efpia.eu

If you respond on behalf of an organization, please allocate yourself a name abbreviation to be used as "Stakeholder name" in the comment tables below. If you comment as an individual, please ignore this field and use your full name as your "Stakeholder name".

EFPIA

Please click **here** to be redirected to the guideline text. The public consultation is launched on 1 August 2024 until 31 October 2024.

Those participating in the public 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.

Before submission, a draft of the comments can be saved in the EU Survey tool. Once submitted, comments can be edited (by 31 October 2024) 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 public consultation (for further information, please see EMA's Data Protection Statement below).

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.

---

1. General comments

	General comment
1	We appreciate the opportunity to review the “Concept Paper on the Need for a Reflection Paper on Assessment of Cardiovascular Safety of Oncology Medical Products.” We support the development of a reflection paper focused on optimizing registrational studies in drug development, to align with regulatory requirements and medical guidelines from professional associations. We look forward to reviewing the draft. We recommend including cardio-oncology organizations, such as ICOS and the Cardiac Safety Research Consortium, in the authorship and review process. Cardiovascular (CV) toxicity from oncological treatments is common, with real-world data indicating that approximately one in three patients experiences CV toxicity. Additionally, there is inconsistency in CV toxicity endpoints and assessments in oncology clinical trials. Therefore, it is essential to develop a reflection paper that outlines best practices for CV safety.
2	
3	
4	
5	
6	

2. Specific comments on text

2.1. Introduction

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
1	Line 32	"Allowing them to receive the best antitumor therapy ". This aim should not be short term. We should aim for patients to receive the best antitumor therapy, for an appropriate duration of time with no deleterious effect on PFS/OS	Suggest highlighting the need, when evaluating the CV effects of the drug, to take into account dose reductions, exposure duration and impact on efficacy endpoints in the study (integrated safety/efficacy analysis) as well as plan how to obtain long-term data on drug acceptability (regarding cardiotoxicity)
2			
3			
4			
5			
6			
7			
8			
9			
10			

2.2 Problem statement

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
1	Line 38-41	We suggest using and assessing consistent CV endpoints (e.g., MACE) in cancer clinical trials (e.g., prostate cancer clinical trials)	
2			
3			
4			
5			
6			
7			
8			
9			
10			

2.3 Discussion (on the problem statement)

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
1	Line 41	One concern is the use of parallel toxicity assessment systems. We recommend avoiding multiple grading systems whenever possible, as they hinder reconciliation and limit cross-study comparisons. Although CTCAE has its limitations, refining its use to improve reproducibility — such as providing guidance on consistent reporting of specific cardiotoxicities like decreased cardiac function — can reduce reliance on conflicting grading systems. For instance, many studies monitor CRS or ICANS using ASTCT criteria, which can lead to confusion in data reporting. When the same event is recorded in both CTCAE and ASTCT, reconciling these reports can be nearly impossible.	
2	Line 47	This reflection paper does not point the need to take into account the understanding of the MOA, of CV toxicity (reference to non-clinical data, known class effects) to accurately define CV endpoints	Suggest address knowledge of MOA of the drug leading to CV toxicity when known, and consider recognised class effects when designing studies based on the aspects described in lines 108 to 114
3	Line 55	But all disease settings should be considered, as often drugs are developed in metastatic disease first, then move earlier in the disease setting, potentially curative setting.	We understand that this is lifted from a publication, however, I would focus more on effective minimization of the CV risk by early detection to ensure continued benefit to the patient.
		Another challenge in oncology is the impact of breakthrough therapy and accelerated pathways leading to less safety data, and especially no long-term data, at approval.	

4	Line 64 - 74	RMPs can only be used to manage important risks and does not cover delayed and rare reactions not identified at the end of phase III study.	Could be covered in the reflection paper under RMP implications
5	Line 81	Comment for Health Authority Submission: 1. Prefer further qualification of arrhythmias, as definition include sinus tachycardia, which is multifactorial. There need to be a clarity regarding cardiac and vascular causes of sinus tachycardia. 2. myocardial infarction, stroke, ... peripheral ischemia - suggestion is to bucket them under ischaemic vascular conditions. 3. Vascular (venous) injury - Not sure what risk this denotes.	
6	Line 106	Study duration should be considered post treatment access and how safety data will be collected throughout patient treatment (ensuring more long-term data). CV safety monitoring should include mitigation measures, when a CV toxicity occurs (therapeutic management guidelines, cardioprotective treatment to be proactively introduced in some at-risk populations, ...) as well as modalities and frequency of monitoring. Consideration of the impact of CV safety monitoring should be made mandatory in CT, for all trial populations, with requirements to include them in the label should be anticipated, and appropriate a priori analysis in patients with different cardiac risk factors planned.	More details on what each of these aspects would need to cover in the reflection paper may be useful.

7	Line 107 -108: …which will be tailored to the different potential scenarios Selection of populations: inclusion/exclusion criteria, collection of CV risk factors.	Consider adding a general recommendation about scenario-dependent dose modification and management of CV toxicities; e.g., per CTCAE grade or recurrence. 'Collection of CV risk factors' is not only part of selection of populations but can be separately captured as 'baseline data collection'. Recommendation to add definition of CV risk factors; e. g., what constitutes a drug induced cardiac adverse effect? Consider adding specifics such as 'may include considerations of grouping terms for the common CV toxicities.' Original text (bullet point): "The proposed reflection paper is planned to cover the following aspects, which will be tailored to the different potential scenarios: […] Prospective definition of CV endpoints and analysis."	Dose modification and management of CV toxicities. e. g. per CTCAE grade or recurrence
		Consider adding specifics such as 'may include considerations of grouping terms for the common CV toxicities.' Original text (bullet point): "The proposed reflection paper is planned to cover the following aspects, which will be tailored to the different potential scenarios: […]	

Prospective definition of CV endpoints and analysis."

Specific cardiovascular (CV) toxicity-related safety endpoints are warranted in certain contexts; however, it is debatable whether this should be implemented across all oncology drug development.

Long safety follow-up: cardiovascular side effects may occur years after completing therapy. Capturing these long-term effects requires extended follow-up periods, which can be logistically challenging. We recommended systematic evaluation of the contexts in which long-term follow-up should be contemplated.

Pre-existing condition: many oncology patients may already have cardiovascular risk factors or diseases before starting cancer treatment. This makes it difficult to distinguish whether a CV event is due to the cancer therapy or underlying conditions.

Diverse population: cancer trials often include a diverse group of patients in terms of age, gender, and comorbidities, leading to variability in cardiovascular risk. Stratifying patients based on their baseline CV risk adds complexity to the analysis but may be necessary.
Balancing between endpoints: balancing the assessment of both oncologic (PFS and OS) and CV outcomes can be challenging, especially in terms of study design and endpoint prioritization, as CV events may compete with these outcomes, particularly in long-term follow-up.

We look forward to the discussion of these points and

8	Line 110-112: Prospective definition of CV endpoints and analysis. & safety monitoring during registration trials.	welcome the opportunity, if possible, to participate in it. CV safety monitoring during registration trials. Will 'CV safety monitoring' cover recommendation of labs/ECGs needed for CV toxicities in general and specifically? We suggest that it would be advisable to do so. We suggest considering which elements of CV safety should be mandatory, such as the collection and analysis of cardiovascular adverse events in all prostate cancer studies. Original text (bullet point): “The proposed reflection paper is planned to cover the following aspects, which will be tailored to the different potential scenarios: […] Reporting of CV outcomes.” CV outcomes are always reported as adverse events (AEs) even if these events are expected based on the mechanism of action. All treatment emergent AEs are analyzed and based on the seriousness criteria. These AEs are reported to respective Agencies. That being the case, we look forward participating, if possible, in discussions about how the system can be modified to increase its utility. The reflection paper should also consider a discussion of the use of real-world data (RWD) as an external control arm, to provide background rates of CV events	Prospective definition of CV endpoints and analysis which may include considerations of grouping terms for the common CV toxicities. Text reinforcing the collection and analysis of CV AEs in prostate cancer studies.	

under standard-of-care therapy, given that many trials are single arm within the oncology therapy area.

Balancing between endpoints: balancing the assessment of both oncologic (PFS and OS) and CV outcomes can be challenging, especially in terms of study design and endpoint prioritization, as CV events may compete with these outcomes, particularly in long-term follow-up.

We look forward to the discussion of these points and welcome the opportunity, if possible, to participate in it.
CV safety monitoring during registration trials.

Will 'CV safety monitoring' cover recommendation of labs/ECGs needed for CV toxicities in general and specifically? We suggest that it would be advisable to do so.

We suggest considering which elements of CV safety should be mandatory, such as the collection and analysis of cardiovascular adverse events in all prostate cancer studies.

Original text (bullet point):

“The proposed reflection paper is planned to cover the following aspects, which will be tailored to the different potential scenarios:

[…]

Reporting of CV outcomes.”

		CV outcomes are always reported as adverse events (AEs) even if these events are expected based on the mechanism of action. All treatment emergent AEs are analyzed and based on the seriousness criteria. These AEs are reported to respective Agencies. That being the case, we look forward participating, if possible, in discussions about how the system can be modified to increase its utility.	
9	106-114	For example, a well-designed and executed global prostate cancer CV AE registry, would be expected to generate informative insights. Comment for Health Authority Submission: Recommendation to add Post-Marketing Commitments. Consider adding a bullet for 'CV signal assessment' prior to Labelling implications'.	Add 'CV signal assessment'
10			

2.4 Recommendation

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			

2.5 Proposed timetable

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			

2.6 Resource requirements for preparation

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			

2.7 Impact assessment (anticipated)

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			

2.8 Interested parties

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			

2.9 References to literature, guidelines, etc.

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			

Other comments

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			

Thank you for your contribution.

Contact

Contact Form