EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 January 2026
EMA/8699/2026
Committee for Human Medicinal Products (CHMP)

# Reflection Paper on investigation and assessment of cardiovascular safety of anticancer medicinal products

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| Agreed by the Cardiovascular Working Party | 14 Nov 2025 |
| Agreed by the Oncology Working Party | 7 Nov 2025 |
| Adopted by CHMP for release for consultation | 19 January 2026 |
| Start of public consultation | 22 January 2026 |
| End of consultation (deadline for comments) | 31 July 2026 |

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

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| Keywords | Cardiovascular safety, oncology, anticancer medicinal products, anticancer drugs |

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# 1. Introduction

The European Medicines Agency (EMA) have established in the past general recommendations for the assessment of cardiovascular (CV) safety in drug development [1], and for general assessment of safety of anticancer medicinal products [2]. The International Council for Harmonization (ICH) also provides standardized regulatory guidelines with general recommendations for the assessment of non-clinical [3,4] and clinical safety of medicinal products for human use [5,6]. However, none of these documents has focused specifically on the assessment of CV safety of medical products for the treatment of people living with cancer. This has become increasingly important due to the rising incidence of CV toxicities associated with cancer therapies due to several factors. These including the increased age at which cancer treatment is received, the presence of concomitant CV risk factors, and the emergence of anticancer medicinal products with new mechanisms of actions associated with relevant CV side effects [7-10]. Approximately one in three patients undergoing cancer treatment experiences CV toxicity, which poses significant challenges for both patients and healthcare providers [10]. Both the positive long-term impact of anticancer medicinal products and the growing shift from palliative care to adjuvant therapies with drugs known to carry cardiovascular risks significantly affect cardiovascular safety. Assessing cardiovascular (CV) safety in oncology trials is challenging due to several factors. There is often lack of comprehensive baseline CV toxicity risk assessment, strict inclusion/exclusion criteria that poorly represent patients at the highest risk of developing CV toxicity, and the presence of previous exposure to other therapies that may also be associated with CV toxicity [9]. In addition, many oncology trials are characterized by relatively small sample sizes, the absence of a control group, and differential follow-up between experimental and control arms in comparative trials. The purpose of this reflection paper, developed in collaboration between the EMA Cardiovascular Working Party (CVSWP) and the Oncology Working Party (ONCWP) following the adoption of the corresponding concept paper in 2024 [11], is to provide recommendations for the planning, data collection, and evaluation of CV safety of anticancer medicinal products, taking into account the unique aspects of anticancer treatments, patient populations, and trial designs.

A tailored, risk-based approach is recommended, characterized by two extremes of CV risk. At the lower end, risk is considered minor for new anticancer medicinal products belonging to a well-established pharmacological class with no known CV safety concerns. At the higher end, risk is considered substantial when the investigational product represents a novel pharmacological class or mechanism of action and is supported by non-clinical evidence indicating potential CV toxicity, or by CV safety signals emerging during clinical development. As a part of the risk-based approach, which relates to (1) generating evidence and (2) assessing evidence, a strategy based on the totality of evidence should be adopted that would account for the variability of clinical settings that the investigational anticancer medicinal product is intended for. Specific considerations should be given to the cancer's type, stage and intended place in therapy (i.e. adjuvant versus non-adjuvant therapies) of the intended drug, that ultimately impact on life expectancy and, in turn, the likelihood of CV toxicity manifesting.

For those medicinal products with a substantial risk and for those products where the risk category could not be easily assigned (for example due to the novelty of the class, very limited early clinical exposure), a more detailed assessment of CV safety is warranted that should be considered at the planning stage of the registration trial, in order to better estimate the overall clinical effect of the medicinal product in the intended population. For the low-cardiac risk category of anticancer products, safety monitoring during clinical experimentation supported by a clinical and nonclinical evaluation of the QT/QTc interval prolongation and pro-arrhythmic potential may suffice, unless CV safety signals do emerge that would require further characterization.

It is expected that the systematic approach recommended in this document for collecting, assessing, and managing CV toxicity in oncology trials will enhance participant safety through earlier detection and management of CV events during the trials. It will also promote an adequate profiling of a given treatment-related cardiotoxicity that can inform an appropriate risk-based strategy to be applied in the post-marketing setting for a safer use of the medicinal product in the intended population. Ultimately, this approach will allow for balancing the risk of cancer treatment-related CV toxicity (CTR-CVT) against the absolute benefit of the cancer treatment and will facilitate easier comparison between different treatment approaches in the intended indication.

# 2. Scope

This reflection paper aims to address the lack of uniformity in CV toxicity endpoints, the characterization of baseline CV risk, and the monitoring, assessment, and follow-up of CV safety in oncology studies. It will cover various aspects of CV safety assessment, including the selection of populations, study design, prospective definition of CV endpoints, CV safety monitoring, baseline data collection, management of CV toxicities, reporting of CV outcomes, and implications for Risk Management Plans (RMP) and labelling [11]. Following a risk-based approach, this reflection paper is applicable to all new anticancer medicinal products being developed in the oncology setting where there is a potential risk of CV toxicity.

# 3. Legal Obligations and Regulatory Requirements

This reflection paper should be read in conjunction with the following documents:

- Reflection paper on assessment of cardiovascular safety profile of medicinal products (EMA/CHMP/50549/2015)
- Guideline on the clinical evaluation of anticancer medicinal products (EMA/CHMP/205/95 Rev.6, 5 January 2019)
- ICH S7A Note for guidance on safety pharmacology studies for human pharmaceuticals (CPMP/ICH/539/00, June 2001)
- ICH E14/S7B Clinical and Non-clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential – Questions and Answers (EMA/CHMP/ICH/415588/2020)
- ICH S7B The non-clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals (CPMP/ICH/423/02)
- ICH E2A Clinical safety data management: definitions and standards for expedited reporting (CPMP/ICH/377/95).
- ICH guideline E2F on development safety update report (EMA/CHMP/ICH/309348/2008)
- ICH E9(R1) Addendum on estimands and sensitivity analysis in Clinical trials to the guideline on statistical principles for Clinical trials (EMA/CHMP/ICH/436221/2017).

# 4. Selection of Populations

## Inclusion/exclusion criteria

The selection of appropriate populations for oncology trials is critical for accurately assessing CV safety. Inclusion and exclusion criteria should consider baseline CV risk factors, previous exposure to cardiotoxic therapies, and the presence of underlying CV disease and other comorbid conditions [12]. Trials should aim at including a diverse group of patients in terms of age, gender, and comorbidities to ensure the external validity and generalizability of the findings of the trials.

The inclusion criteria should ensure that patients with pre-existing CV conditions are not excluded unless appropriately justified based on identified safety concerns, in order to avoid a potential underestimation of the CV risks associated with the treatment. On the other hand, exclusion criteria should be carefully defined to avoid including patients who are at an excessively high risk of CV events in order to protect them from potential serious consequences.

## Baseline assessment of CV risk factors

The study design should include a comprehensive baseline assessment of CV risk factors, including clinical history, physical examination, laboratory tests and imaging studies [7,8,12,13]. This characterisation may be necessary to help to identify patients who are at a higher risk of developing CV toxicities and allow for appropriate monitoring and management during the trial (see also section 8), and also to accurately assess the impact of oncology treatments on CV outcomes across relevant subgroups [7]. Standardized data collection forms and electronic case report forms (eCRFs) can facilitate consistent and accurate baseline data collection.

Key risk factors such as hypertension, diabetes, dyslipidaemia, and previous CV disease should be documented and considered in the analysis of CV safety data. Additionally, it is important to consider genetic predispositions that may affect individual responses to cancer therapies. For example, certain genetic markers have been associated with increased susceptibility to cardiotoxicity from specific treatments. Notably, variants in genes such as RARG, SLC28A3, UGT1A6, NAT2, and CYP2D6 have been associated with heightened risk of cardiotoxicity, particularly in the context of therapies involving trastuzumab and anthracyclines [7]. Incorporating genetic screening into inclusion/exclusion criteria could help identify high-risk patients and tailor treatment plans accordingly. Beyond biomarkers [13], imaging techniques, such as echocardiography, cardiac magnetic resonance imaging (MRI) and computed tomography angiography (CTA), can provide detailed information on the structural and functional status of the heart [7,8,12]. These imaging modalities can help to identify subclinical CV abnormalities that may not be detected through routine clinical assessments. The integration of these advanced imaging techniques into baseline assessments can enhance the accuracy of CV risk stratification and improve the overall assessment of CV safety in oncology trials.

# 5. Study Design, Duration

The design and duration of oncology trials should be appropriate to capture both short-term and long-term CV toxicities depending on the target indication. Randomized controlled trials (RCTs) with adequate sample sizes and appropriate control groups are the optimal strategy for robust CV safety assessment [7,8]. The duration of follow-up should be sufficient to capture late-onset CV events, which may occur years after the completion of cancer therapy. To this end, a risk-based approach should be

adopted to define specific CV monitoring and adequate risk mitigations measures to be applicable post-marketing (see section 11).

It is recognised that balancing the assessment of both oncologic [progression free survival (PFS) and overall survival (OS)] and CV outcomes can be challenging, especially in terms of study design and endpoint prioritization, as trials in this setting will be primarily designed to demonstrate the efficacy and safety of the new anticancer medicinal product in oncologic outcomes. In addition, one has to bear in mind that some CV events may compete with these outcomes, particularly CV death with OS.

Extended follow-up periods and the use of real-world data (RWD) as external control arms, when clinical trials have followed a single-arm design, could provide valuable insights into the long-term CV safety of anticancer treatments if the methodology used is pre-defined and scientifically sound. Adaptive trial designs may enable researchers to adjust sample sizes, treatment arms, treatment doses, or endpoints and even the expansion of trial eligibility to a broader population based on interim efficacy or safety that provide to do so without compromising the integrity of the trial [14]. However, adaptive designs are particularly challenging and usually discouraged in single-arm trials (SATs) mentioned before. Regarding CV safety, treatment doses may be reduced or inclusion/exclusion criteria tightened to protect patient's subgroups that have experienced CV events during the course of the trial. Conversely, eligibility may be broadened to include patients with CV risk factors or a history of CV disease if interim analyses demonstrate no increased CV risk [14].

# 6. Definition of CV Endpoints, Reporting and Analysis

## Definition of CV endpoints

Prospective definition and standardized classification of CV endpoints are crucial for consistent and reliable assessment of CV safety in oncology trials.

The International Cardio-Oncology Society (ICOS) [15] provided consensus definitions for the most commonly reported CV toxicities, grouped into eight areas, which include:

a) **Cardiac dysfunction/heart failure** [e.g., induced by anthracyclines, human epidermal growth factor receptor 2 (HER2) targeted agents];
b) **Myocarditis** [e.g., induced by anthracyclines (e.g.: doxorubicin), antimetabolites (e.g.: fluorouracil), alkylating agents (e.g.: cyclophosphamide), and immune checkpoint inhibitors (ICIs)];
c) **Arrhythmias/QT prolongation** [e.g., associated with arsenic trioxide, some tyrosine kinase inhibitors (TKIs) targeting the breakpoint cluster region-Abelson (BCR-Abl) oncogene locus, and cyclin-dependent kinase (CDK) 4/6 inhibitors like ribociclib];
d) **Hypertension** [e.g., induced by targeted agents such as vascular endothelial growth factor TKIs (VEGF-TKIs), the proteasome inhibitor carfilzomib, mTOR (mammalian Target of Rapamycin) inhibitors, TKIs targeting the B-raf (rapidly accelerated fibrosarcoma) protein kinase (BRAF), the mitogen-activated protein/extracellular signal-regulated kinase (MEK), and Bruton's tyrosine kinase (BTK)];
e) **Vascular toxicity**, including myocardial infarction, stroke, transient ischemic attack, venous thromboembolic event, arterial thromboembolism, peripheral ischemia, vasculitis, vascular disorder, and venous injury (e.g., some of them associated with targeted therapies like CAR-T, VEGF-

TKIs, TKIs targeting the BCR-Abl fusion protein, such as nilotinib and ponatinib, and the epidermal growth factor receptor inhibitor erlotinib);

f) **Valvular heart diseases** (e.g., anthracyclines like doxorubicin, anti-HER2 agents like trastuzumab, and some chemotherapy drugs like cyclophosphamide and ifosfamide have been associated with heart valve problems);

g) **Pulmonary hypertension** (e.g., chemotherapeutic agents like bleomycin, mitomycin, and cyclophosphamide, as well as TKIs such as dasatinib, immunomodulatory agents like interferons, and some proteasome inhibitors such as carfilzomib, have been linked to this side effect); and

h) **Pericardial diseases** [anthracyclines, alkylating agents (e.g.: cyclophosphamide), antimetabolytes (e.g.: cytarabine), and the antitumor antibiotic bleomycin are known to cause pericarditis, while TKIs like dasatinib, as well as the trans retinoic acid differentiation agent and the alkylating agent busulfan, have been associated with pericardial effusions).

According to the expected safety profile of the product, based on safety pharmacology and pharmaceutical class, predefined specific CV events should be included in the protocol as adverse events of special interest (AESI). These endpoints should be defined according to consensus definitions, from cardiology and oncology societies, and explicitly mapped to Common Terminology Criteria for Adverse Events (CTCAE) [16] for summary purposes.

The use of validated biomarkers, imaging techniques, and clinical assessments can enhance the accuracy of CV endpoint determination [7,13].

Moreover, the prospective definition of CV endpoints, ideally tailored to the expected safety profile of each specific product, should include both clinical and subclinical events. Clinical events, such as myocardial infarction, heart failure, and arrhythmias, are typically easier to identify and classify. However, subclinical events, such as changes in cardiac biomarkers or imaging findings, can provide early and more sensitive indications of cardiotoxicity and could potentially help to prevent more serious clinical events [7]. The inclusion of both types of endpoints in the analysis will provide a more comprehensive assessment of the CV safety profile of the anticancer medicinal product.

## Reporting of CV outcomes

Consistent and transparent reporting of CV outcomes is essential for the evaluation of CV safety in oncology trials. All CV events should be reported as adverse events (AEs), with detailed documentation of the event severity, timing, and management [8]. The use of standardized reporting templates and electronic data capture systems can enhance the accuracy and completeness of CV outcome reporting.

Moreover, the reporting of CV outcomes should include both clinical and sub-clinical events [7]. Clinical events, such as myocardial infarction, heart failure, and arrhythmias, should be reported with detailed information on the timing, severity, and management of the event. Subclinical events, such as changes in cardiac biomarkers or imaging findings, should also be reported to provide a comprehensive assessment of the CV safety profile of the anticancer medicinal product. The inclusion of both types of events in the reporting will help to identify early signs of cardiotoxicity and allow for timely intervention to prevent more serious clinical events. Meta-analyses and pooled data analyses can provide valuable insights into the overall CV safety profile of anticancer treatments [8]. For that purpose, a pre-specified safety meta-analysis of CV endpoints should be considered for anticancer medicinal products with a substantial risk of CV adverse effects. This implies that systematic assessment as well as consistency of definitions of CV endpoints would be sought/maintained across the trials in order to strengthen the quality of the data available for B/R assessments.

### Analysis of CV outcomes

Pre-specified analyses of CV outcomes, considering both investigator-reported data and adjudicated events is recommended whenever feasible. However, it should be acknowledged that such analyses will often be exploratory in nature and underpowered for the less frequent serious CV events. [8]. Additionally, machine learning algorithms could be employed to analyse large datasets, whenever available, and identify patterns or predictors of CV toxicity, but this approach needs further validation [7]. While the use of artificial intelligence (AI) is emerging for signal detection in pharmacovigilance activities (see section 8 and [18]), future work will need to assess the role of AI in the ascertainment and characterization of safety events in clinical trials [8].

## 7. CV Safety Monitoring and Management of CV toxicities During Registration Trials

### CV safety monitoring

Continuous CV safety monitoring during registration trials is essential to detect and manage CV toxicities promptly [7,8]. This includes regular assessments of cardiac biomarkers, electrocardiograms (ECGs), and imaging studies. Monitoring protocols should be tailored to the specific anticancer treatment and patient population, with predefined thresholds for intervention and dose modification based on the severity of CV events. To address potential differential follow-up between treatment arms in registration clinical trials, it is recommended to include post-treatment monitoring after the end of treatment. Such monitoring should be standardized across study arms to ensure consistency in data collection and outcome assessment. In addition, post-trial treatment regimens should be documented and, when possible, integrated into the analysis, as these may influence long-term safety and efficacy outcomes.

Multidisciplinary collaboration between oncologists, cardiologists, and other healthcare providers is crucial for effective CV safety monitoring and management. Moreover, wearable devices that continuously monitor cardiac function can provide real-time data on patient health status during trials. These devices offer a non-invasive means to track changes in cardiac biomarkers or ECG readings over time, allowing for early detection and intervention in case of adverse events [17].

### Management of CV toxicities

In addition to regular monitoring, it is important to establish clear protocols for the management of CV toxicities during the trials. This includes guidelines for dose modification, treatment interruption, or discontinuation based on the severity of the CV event [7]. These have also a bearing on the efficacy analyses as intercurrent events, considering E9(R1). This information needs to be further included in the product information, as it is essential to make informed decisions about the use of anticancer treatments (see also section 8). Furthermore, developing personalized treatment plans based on individual patient risk factors and responses to therapy can help to optimize the management of CV toxicities [7].

The management of CV toxicities in oncology patients requires a risk-based and individually tailored approach, including dose modification and supportive care based on the severity and recurrence of CV events [7]. The CTCAE grading system [16] can guide the management of CV toxicities, with specific

recommendations for dose reduction, interruption, or discontinuation of cancer therapy, and the use of cardioprotective agents, such as beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and statins that can help to mitigate some types of CV toxicity associated with cancer therapies should be outlined in the trial protocol [7].

# 8. Risk Management Plan (RMP) Implications, including Labelling Implications in Safety

While some CV events may be easily identifiable, as they occur in the short term [e.g.: acute heart failure after anthracyclines, trastuzumab or chimeric antigen receptor T cell (CAR-T) therapies, hypertension under treatment with vascular endothelial growth factor inhibitors (VEGFi)] [7], in other cases they become clinically evident only after the CV system has been exposed to a drug/metabolite over a prolonged period or even years after exposure. Others are so rare that a safety signal requires thousands of patients exposed. Regulatory agencies are working to improve methods for the identification of emerging safety signals. Some of the approaches being assessed rely on incorporation of artificial intelligence and data from a combination of active and passive safety surveillance systems [8,18].

In the evaluation of contemporary anticancer medicinal products, more than 1 in 4 have required a safety warning related to cardiotoxic effects, including more than 40% of the targeted and immune-based drugs [19]. In post-marketing experience, there is a delayed recognition of cardiotoxic effects, which is concerning, particularly given the rapid emergence of many targeted and immune-based cancer therapies, and the potentially devastating consequences of CV toxicity events [19]. In cases for which it is difficult to delineate the CV safety profile of the new compound before authorization, these uncertainties should be managed under the RMP [20].

The RMP should include the identified and potential risks and the need for additional Risk Minimization Measures (aRMM), as well as detailed guidelines for the management of CV toxicities, including recommendations for baseline assessments, regular monitoring, and intervention strategies. The labelling of anticancer medicinal products should clearly outline the potential CV risks associated with the treatment [21] and provide guidance on the management of these risks. This information is essential for healthcare providers to make informed decisions about the use of anticancer treatments and to implement appropriate monitoring and management strategies to minimize the impact of CV toxicities on patient outcomes. Data to support this information needs to be available at the time of the marketing authorisation. Post-marketing surveillance and RWD can further inform the RMP and support the safe use of anticancer medicinal products in clinical practice.

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# 10. List of abbreviations

| | |
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| **AEs**: | Adverse Events |
| **ACE:** | Angiotensin-converting enzyme |
| **aRMM:** | additional Risk Minimisation Measures |
| **BCR-Abl:** | Breakpoint cluster region protein-Abelson proto-oncogene fusion protein |
| **BNP**: | B-type Natriuretic Peptide |
| **BRAF:** | human gene that encodes the B-Raf protein (rapidly accelerated fibrosarcoma) |
| **CAR-T**: | Chimeric Antigen Receptor T cell |
| **CDK**: | Cyclin-dependent kinase |
| **CHMP**: | Committee for Medicinal Products for Human Use |
| **CI**: | Confidence Interval |
| **CTA:** | Computed tomography angiography |
| **CTCAE**: | Common Terminology Criteria for Adverse Events |
| **CV**: | Cardiovascular |
| **CTR-CVT**: | Cancer Treatment-Related Cardiovascular Toxicity |
| **ECRF:** | Electronic case report form |
| **ECG**: | Electrocardiogram |
| **EMA**: | European Medicines Agency |
| **ESC**: | European Society of Cardiology |
| **EUSurvey**: | European Union Survey |
| **FDA**: | U.S. Food and Drug Administration |
| **HER2**: | Human Epidermal Growth Factor Receptor 2 |
| **HFA**: | Heart Failure Association |
| **ICIs**: | Immune Checkpoint Inhibitors |
| **ICH**: | International Council for Harmonization |
| **ICOS**: | International Cardio-Oncology Society |
| **MRI**: | Magnetic Resonance Imaging |
| **mTOR:** | mammalian Target of Rapamycin |
| **NT-proBNP**: | N-terminal pro-BNP |
| **OS**: | Overall Survival |
| **PFS**: | Progression-Free Survival |
| **RMP**: | Risk Management Plan |
| **RWD**: | Real-World Data |
| **TKIs**: | Tyrosine Kinase Inhibitors |
| **VEGFi**: | Vascular Endothelial Growth Factor Inhibitors |