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PRIMERS IN CARDIO-ONCOLOGY

Cardiovascular Safety in Oncology Clinical Trials

JACC: CardioOncology Primer

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ABSTRACT

The development of novel treatments has improved cancer outcomes but may result in cardiovascular toxicities. Traditional approaches to clinical trial safety evaluation have limitations in their ability to detect signals of cardiovascular risk. Mechanisms to increase power and specificity to clarify cardiovascular safety are required. However, implications include increased costs and slower development. The Cardiovascular Safety Research Consortium facilitated stakeholder discussions with representation from academia, industry, and regulators. A think tank was assembled with the aim of providing recommendations for improved collection and reporting of cardiovascular safety signals in oncology trials. Two working groups were formed. The first focuses on incorporation of consensus definitions of cardiovascular disease into the Common Terminology Criteria for Adverse Events used in oncology trial reporting. The second group considers methods for ascertainment and adjudication of cardiovascular events in cancer trials. The overarching aim of this primer is to improve understanding of the potential cardiovascular toxicities of cancer therapies. (JACC CardioOncol. 2025;7:83-95)
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ABBREVIATIONS AND ACRONYMS

AE = adverse events

CSRC = Cardiovascular Safety Research Consortium

CTCAE = Common Terminology Criteria for Adverse Events

FDA = U.S. Food and Drug Administration

ICH = International Council for Harmonization

IC-OS = International Cardio-Oncology Society

HIGHLIGHTS

- Improved cardiovascular event definitions should be used in cancer therapy trials.
- Refinements in safety data ascertainment methods should allow better characterization of potential treatment-associated toxicities.
- Optimal cardiovascular event ascertainment and recording methods may vary depending on drug, development stage, and patient factors.

Acceleration in the development of novel treatments has improved the clinical outcomes for many patients with hematologic and solid malignancies. The mechanisms and targets of these therapies can result in toxicities including cardiovascular, thrombotic, immune-mediated, and metabolic complications among others.[1,2] Established cancer therapies such as anthracyclines are associated with heart failure and cardiomyopathy; vascular endothelial growth factor inhibitors are associated with hypertension; and immune checkpoint inhibitors have been associated with a broad array of immune reactions including the rare, but potentially catastrophic, complication of myocarditis. The nature and incidence of the range of potential cardiovascular toxicities may either not be predictable or recognized in preclinical studies. For example, although tyrosine kinase inhibitors may be designed principally to act at a specific target, there is increasing recognition that these drugs can have unintended effects on diverse pathways with consequences including adverse cardiovascular effects. These issues may only become apparent when the drugs are used clinically, and potentially exacerbated by pre-existing cardiovascular risk factors and disease. Pivotal clinical trials may exclude patients at heightened cardiovascular risk and typically have not been representative of the broader population with under recruitment of populations that have faced inequities in care.[3-5] Indeed, the frequent coexistence of both cardiovascular disease and cancer has led to a growing call for a consistent and systematic approach to evaluating cardiovascular safety in clinical trials of cancer therapeutics.[6-8] Although registries offer observational insights, understanding the mechanism of action of the cardiovascular toxicities of specific therapies requires a systematic approach within randomized assessments of efficacy and safety.[7,9-12]

Oncology drug development has progressed at a rapid pace. There are over 3,500 compounds with potential anticancer effects in development,[13] and in 2022 alone, the U.S. Food and Drug Administration (FDA) approved 12 novel anticancer drugs and biologics,[14] while 12 were approved by the European Medicines Agency.[15] These rapid advances have had a major impact upon cancer outcomes with over two-thirds of patients treated for cancer now surviving at least 5 years. The number of cancer survivors living in the United States is projected to reach 22.2 million by 2030.[16] Improved cancer survival means that cardiovascular disease now assumes greater relative importance than it previously did, both during and after cancer therapy. Furthermore, patients with cancer are often at elevated risk of cardiovascular disease because of shared risk factors for cancer and cardiovascular disease. The development of targeted anticancer therapies has illuminated the overlap between mechanistic pathways that are relevant to the pathophysiology of tumor growth, but also necessary for normal cardiovascular function.[17]

The primary focus of most oncology therapeutic trials is anticancer efficacy. However, with the success of cancer treatments, there is a need to improve methods for determining and assessing cardiovascular safety in these trials, as well as minimizing the effects of these cardiotoxicities on patients, including in long-term survivors.[18] In addition, there is a need

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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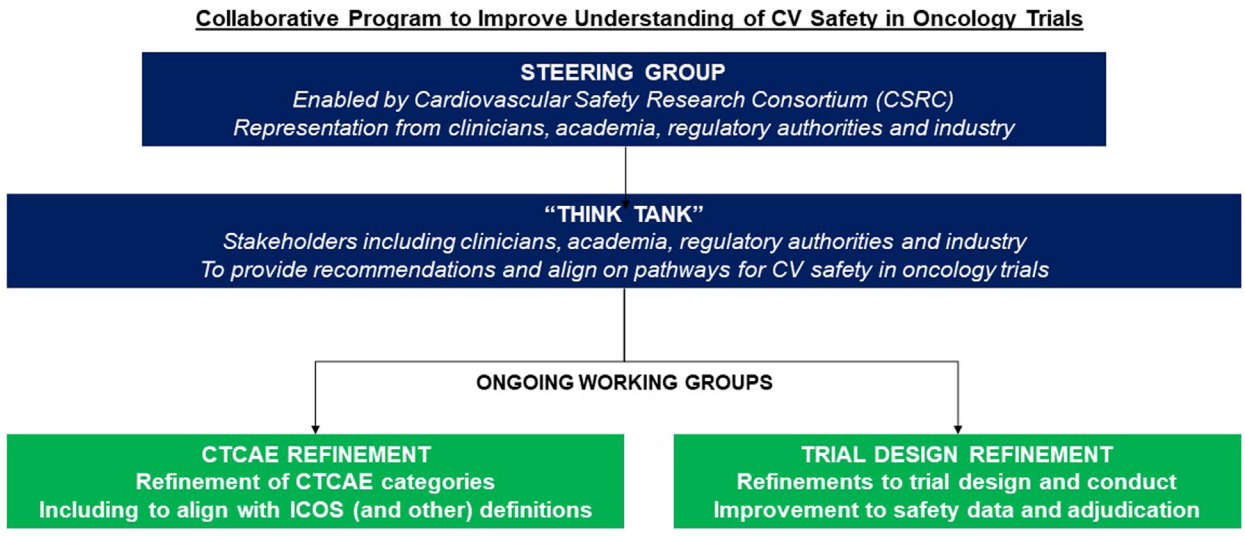
FIGURE 1 CSRC Approach to Cardiovascular Safety for Novel Therapeutics in Oncology



Schema of the CSRC Think Tank approach to discussing and understanding issues related to cardiovascular safety of novel therapies for cancer patients using a collaborative Think Tank and working group approach. CSRC = Cardiac Safety Research Consortium; CTCAE = Common Terminology Criteria for Adverse Events; CV = cardiovascular; IC-OS = International Cardio-Oncology Society.

to have broader representation and diversity of comorbidity, race, and ethnicity.[3-5]

To address these broad-based issues, a multistakeholder think tank was organized through the Cardiac Safety Research Consortium to enable a collaborative discussion and initiate work streams to provide such an approach (Figure 1). The following document outlines the findings of the initial Think Tank and ongoing work streams. The goals and objectives were to provide recommendations for future work for collaborative approaches to improving the collection and reporting of cardiovascular safety in oncology trials.

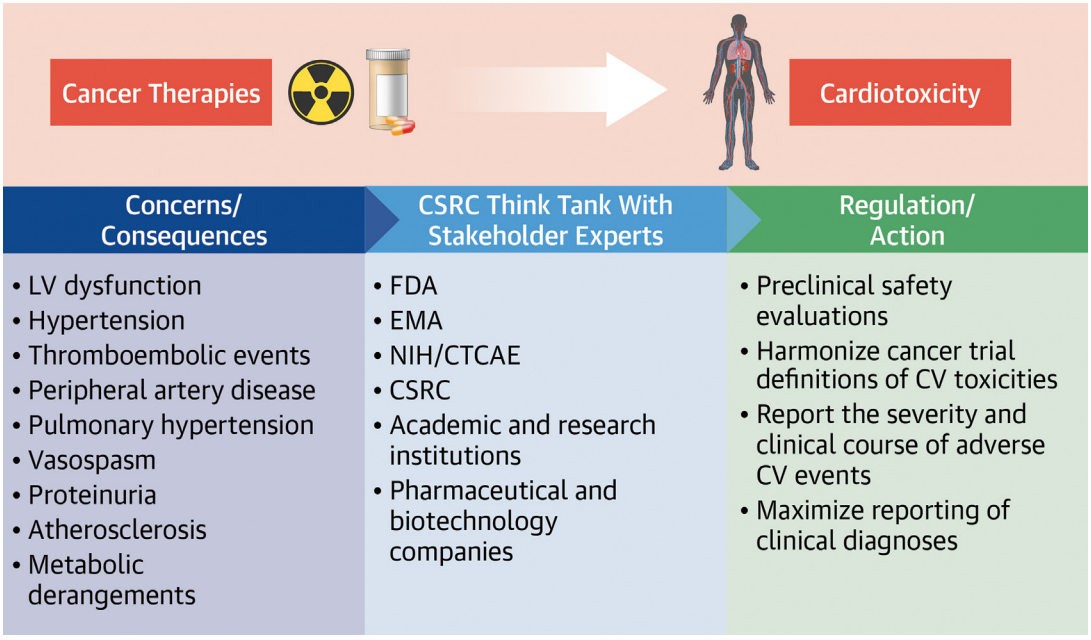
THE ROLE OF THE CARDIAC SAFETY RESEARCH CONSORTIUM AND CARDIO-ONCOLOGY THINK TANK

The Cardiac Safety Research Consortium (CSRC),[19] a public private partnership, was formed in 2005 as a Critical Path Program and formalized in 2006 under a memorandum of understanding between the FDA and Duke University.[20] The mission of the CSRC is to advance regulatory science specifically related to cardiac safety issues across interested stakeholders.

The first CSRC Think Tank concerning Oncology Drug Development (Detection, Assessment, and Risk Mitigation of Cardiac Safety Signals in Oncology Drug Development, October 24-25, 2017) brought together experts from academic organizations (including Vanderbilt University, Ottawa University, University of Pennsylvania, Northwestern University, Georgetown University/Medstar Health, Memorial Sloan Kettering, and Mayo Clinic), research institutes (eg, Duke Clinical Research Institute), pharmaceutical companies (eg, Roche, Eli Lilly, Ducks Flats Pharma, AbbVie, Genentech, Bristol Myers Squibb, CTI Biopharma, and Zogenix), contract research organizations (eg, Quintiles, Icon, ACI Clinical, and Medpace), and members of the FDA and cardiac safety consultants.[21] The think tank raised awareness of the emerging regulatory concerns regarding cardiovascular safety issues from radiation, chemotherapies, and targeted treatments. The safety issues discussed included hypertension, venous and arterial thromboembolic events, peripheral artery disease, pulmonary hypertension, vasospasm, proteinuria, accelerated atherosclerosis, and metabolic derangements.[22]

The second think tank (Cardiovascular Safety in Oncology Clinical Trials: Providing cardiovascular clarity for a new era of cancer therapeutics, December 1, 2021) assembled multi-stakeholder experts from the CSRC, academia (eg, University of Colorado, Harvard Medical School, and University of Glasgow), industry, regulatory groups (eg, FDA, European Medicines Agency, National Institutes of Health, and others)[23] to define a framework to assess

CENTRAL ILLUSTRATION **Concept of the Collaborative Think Tank for Considering Cardiovascular Safety in Trials of Cancer Therapies**



Bonaca MP, et al. JACC CardioOncol. 2025;7(2):83-95.

This figure depicts the process of the collaborative think tank for considering cardiovascular safety in trials of cancer therapies.
CSRC = Cardiovascular Safety Research Consortium; CTCAE = Common Terminology Criteria for Adverse Events; CV = cardiovascular; EMA = European Medicines Agency; FDA = U.S. Food and Drug Administration; NIH = National Institutes of Health; LV = left ventricular.

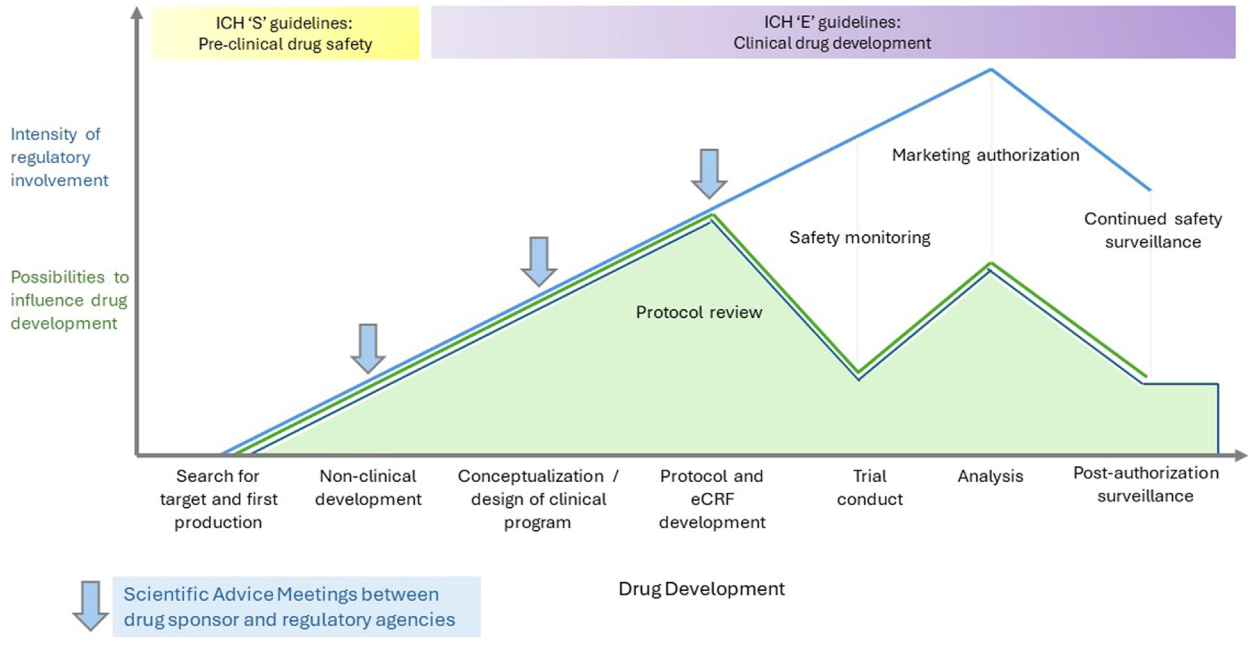
cardiovascular safety issues in oncologic trials, especially in the era of immuno-oncology (**Figure 1, Central Illustration**, Supplemental Figure 1). Whereas the first think tank and paper was created with the goal of creating awareness, this second think tank was brought together with a goal of outlining clear recommendations for ascertainment of cardiovascular safety events in oncology trials and to build a collaborative working group for ongoing development of key concepts. A group of potential participants with a breadth of background expertise was identified by the CSRC leadership. They were invited to participate, and to extend the invitation to relevant colleagues, in order to allow a wide-ranging and interactive conversation. An agenda with key topics was created, experts were invited as speakers, and working groups were created. All elements of the activities were open and inclusive to those that expressed interest. Although the think tank did not directly include patient or community feedback, this is planned in future activities.

REGULATORY CONTEXT

Regulatory bodies are mandated to monitor and guide the development of safe and effective new drugs (**Figure 2**). To achieve greater harmonization in the interpretation and application of technical guidelines, as well as in drug development requirements and regulatory approvals, the International Council for Harmonization (ICH) developed standardized regulatory guidelines. This group was initiated by stakeholders from Europe, the United States of America, and Japan, and is now a wide international collaboration.[24]

ICH 'S' guidelines make recommendations on preclinical safety evaluations to support clinical drug development. In line with ICH S9 guidance, standalone preclinical safety pharmacology studies are not currently required to support trials in patients with advanced cancer, and cardiovascular safety assessments may come from more general toxicity studies. This pragmatic approach is designed to

FIGURE 2 **Regulatory Impact on Safety Evaluation**



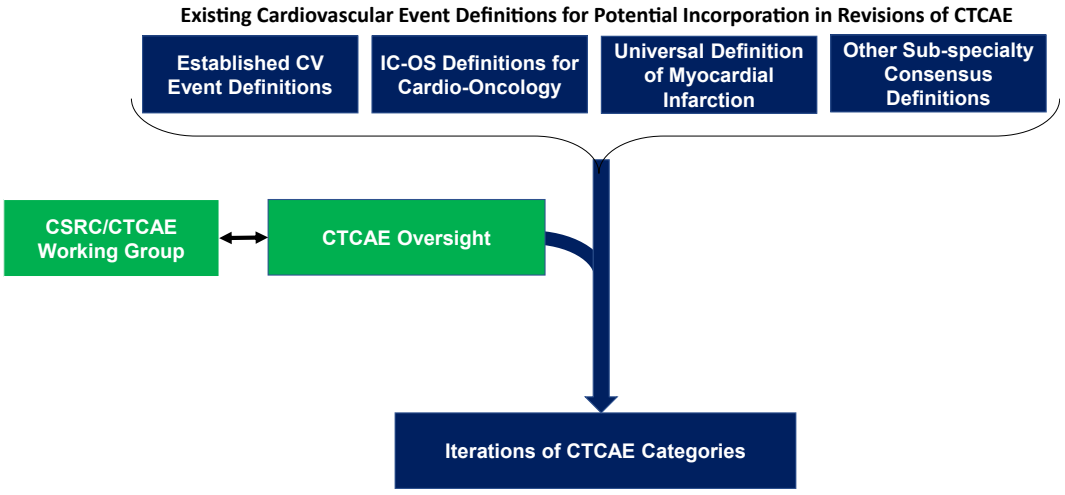
Schema showing the regulatory impact on safety evaluation in oncology trials of the course of drug development activities. The relative possibility for an investigator to influence drug development varies at each stage. Blue line: intensity of regulatory involvement; green line: possibilities to influence drug development.
eCRF = electronic case report form; ICH = International Council for Harmonization.

accelerate the development of anticancer drugs for patients with limited therapeutic options. However, in cases where specific cardiovascular concerns have been identified, dedicated cardiovascular safety studies (as described in ICH S7A and/or S7B) should be considered.

ICH E guidelines make recommendations on clinical drug development. The ICH E2A provides guidance on clinical safety data management. ICH E2F describes cardiovascular adverse events (AE) that are required to be reported as part of the Development Safety Update Report, including electrocardiographic QT-interval assessments. Further guidance (ICH E5 and E7) recognizes the potential for interplay between conditions in special populations (eg, elderly with higher cardiovascular risk) and the safety of trial therapies. Indeed, specific recommendations for human pharmacology studies for cardiotoxicity are provided (ICH E8), including the role of confirmatory studies performed in populations with otherwise under-represented comorbidity, including cardiovascular disease.

Risk assessment during drug development should be conducted in a rigorous manner. However, it is impossible to identify all safety concerns due to limitations such as small sample sizes and short duration of follow-up. This can lead to difficulties in establishing the safety profile in oncology drug products, especially for initial product labeling. Once a drug is marketed, there is usually a large increase in the number of patients exposed, including those with important comorbid conditions. Therefore, post-marketing safety data collection and risk assessment based on observational data are critical for evaluating and characterizing a drug product's risk profile. However, under-reporting of AE remains a critical issue. Regulatory bodies are working to improve methods for the identification of emerging safety signals. The aim is simultaneously to increase precision and to reduce the time taken for recognition of potential adverse effects. Some of the approaches being assessed rely on incorporation of artificial intelligence and data from a combination of active and passive safety surveillance systems. These include the FDA's Adverse Event Reporting System (FAERS)[19] as well as Sentinel, Biologics Effectiveness and Safety (BEST)[25] Systems, and the National Evaluation System for health Technology (NEST).[26] In Europe, a

FIGURE 3 Considerations or Safety Collection Using CTCAE Paradigm



Structure and process flow for consideration of input and refinement of CTCAE safety categories. Abbreviations as in Figure 1.

similar approach has been developed with the EudraVigilance system.[27]

SAFETY ASSESSMENT AND THE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

The National Cancer Institute (NCI) introduced their Common Toxicities Criteria in 1982.[28] Since then, this classification system has evolved to become a ubiquitous safety event assessment tool in oncology therapeutic trials. Renamed in 2003 with v3, Common Terminology Criteria for Adverse Events (CTCAE) provides a severity scale incorporating intended medical intervention and the associated degree of urgency. Of note, due to iterative updates, trials may use multiple versions over time. This grading system is also used in prescribing information to inform the continuation, dose reduction, interruption, or permanent cessation of medicines.

CTCAE STRENGTHS. CTCAE-defined event reporting is a central component of most studies performed under an Investigational New Drug application when reporting to the FDA and other regulatory agencies. Key strengths of CTCAE include its comprehensive nature and usage of Medical Dictionary for Regulatory Activities (MedDRA) terms to allow for ease of reporting to regulatory authorities. CTCAE severity grading has the potential to provide robust and granular data relating to AE, the severity of the adverse cardiovascular effects, and the change with time and treatment. In addition to its importance in the evaluation and reporting of AE and effects in individual trials, consistency in AE reporting severity makes it possible to do reliable meta-analyses for the identification of potential adverse cardiovascular effects that emerge when data are aggregated across studies.

CTCAE LIMITATIONS. Overlap of CTCAE cardiovascular event terms and discordance in severity grading. As CTCAE versions have evolved, new cardiovascular terms have been added. This has introduced issues with overlap between new and pre-existing terms. For example, a patient presenting with asymptomatic left ventricular dysfunction could, based on current CTCAE definitions, fulfill criteria for 4 overlapping AE report terms (left ventricular systolic dysfunction, heart failure, and decline in ejection fraction). This redundancy introduces unnecessary complexity and confusion in reporting. Furthermore, of fundamental importance, the identification of the same magnitude of asymptomatic decline in left ventricular ejection fraction would meet criteria for different severity grades depending upon the term chosen for reporting. The implications of the consequent loss of standardized data as well as the potential for both under- and over-reporting of relevant events are important. Furthermore, definitions for cardiovascular events provided by CTCAE in the

TABLE 1 Challenges in the Optimal Approach to Cardiovascular Event Ascertainment and Categorization in Trials of Cancer Therapies

	Favors Traditional Safety Collection (CTCAE) and Baseline Characterization	Favors Enhanced Safety Collection (eg, Safety Events of Special Interest/Adjudication) and Baseline Characterization	Notes
Drug mechanism	No known or suspected mechanism with cardiovascular toxicity potential	Known or suspected mechanism with cardiovascular toxicity potential (eg, hypertension, prothrombotic, immunotherapy)	Early/preclinical data critical for planning, should be considered in context of known toxicities of existing compounds
Background treatment	No known or suspected mechanism with cardiovascular toxicity potential	Known or suspected mechanism with cardiovascular toxicity potential (eg, hypertension, prothrombotic, immunotherapy)	Important in clarifying background rate related to background treatment and understand if there is effect modification
Population—disease for treatment, eg, type of cancer	Cancer associated with low cardiovascular risk (eg, low thrombosis risk)	Cancer associated with high cardiovascular risk (eg, high thrombosis risk)	Specificity important in differentiating events likely related to cancer versus those that might be related to therapy
Population—cardiovascular risk	Population at low cardiovascular risk (eg, young adults)	Population at high cardiovascular risk (eg, extremes of age, frailty, cardiovascular comorbidities)	Trials designed to include representative populations including with cardiovascular risk encouraged
Phase of study	Early phase	Late phase, in development program planned for multiple populations to enable pooling of data	Although events potentially rare in early phase studies, systematic approach to categorization will enable pooling across studies

cardiovascular category do not always align with "conventional" cardiology definitions.

Reporting of nonspecific terms without link to etiology or final diagnosis. Symptoms such as dyspnea and clinical findings such as edema appear in CTCAE and are commonly reported. CTCAE is not designed to attribute events to an etiology or a final diagnosis, and under- or over-reporting may occur because it remains up to the investigator to report the diagnosis when etiology is determined after initial reporting of symptoms. For example, when edema is reported, it is unclear whether this reflects something relatively inconsequential or whether it is a marker of heart failure, nephrotic syndrome, or hepatic failure. This issue could be circumvented if regulatory bodies and commercial sponsors were to actively seek the underlying diagnosis so that, if an AE is reported initially based on CTCAE symptom categories, this symptom AE should be revised to reporting of a CTCAE diagnostic category/severity report once determined. One major issue is that reporting is often not provided by experts or physicians but by research associates translating from medical records. At times, the expedited nature of reporting may make expert assessment before reporting challenging.

Reporting of isolated biomarker abnormalities without link to etiology or final diagnosis. Classification and reporting of "abnormal" cardiac biomarkers in isolation without a requirement to link to a clinical diagnosis introduces further uncertainty similar to that resulting from reporting of symptoms or physical signs without linkage to final diagnosis. It is acknowledged that reference ranges for cardiac biomarkers are not well-validated in patients with cancer, and cancer per se can be associated with higher circulating concentrations of these.[29] The use of biomarkers in defining adverse cardiovascular events should be taken in the context of the clinical presentation and the results of other diagnostic tests.

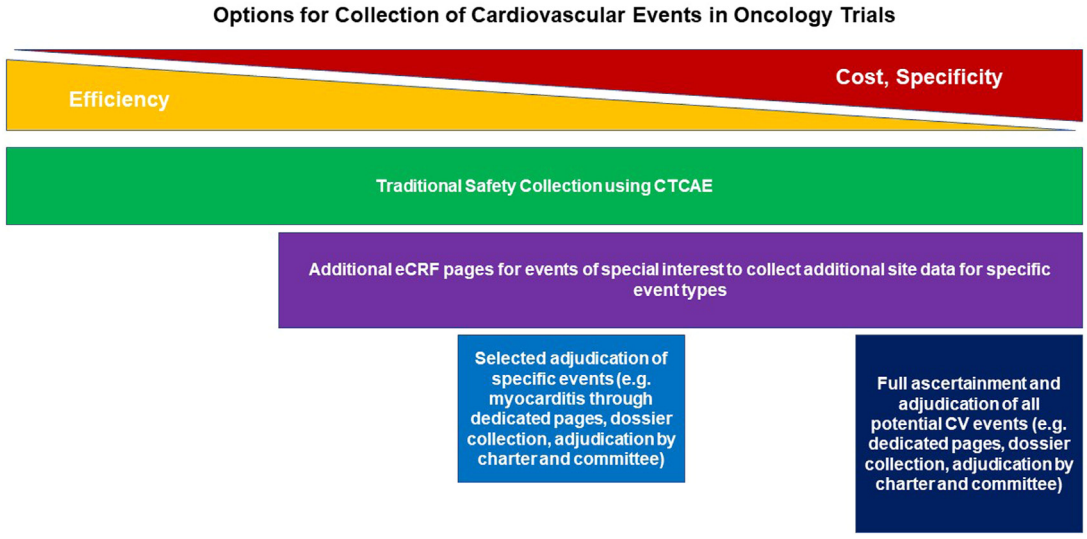
COLLABORATIVE APPROACH TO CTCAE REVISION.

In 2021, the International Cardio-Oncology Society (IC-OS) produced a consensus statement providing definitions of cardiovascular toxicities of cancer therapy.[18] These have been incorporated into the inaugural European Society of Cardiology cardio-oncology guidelines.[30] The development of these definitions was in response to the growing concern about heterogeneity between cardiovascular and oncology society definitions of cardiovascular toxicity from cancer therapies, as well as some of those used in CTCAE.

The timing of both the IC-OS consensus statement and the European Society of Cardiology guideline aligns with the revision of CTCAE version 6. This presents an ideal opportunity for clinicians, regulatory bodies, pharmaceutical industry representatives, and NCI CTCAE staff to collaborate to incorporate contemporary definitions, rationalize reporting terms, and resolve challenges relating to cardiovascular events (**Figure 3**).

In CTCAE version 6, IC-OS cardiovascular toxicity definitions have been incorporated, whereas overlapping event terms have been minimized or eliminated. Severity grading has also been reviewed with input from the multidisciplinary representation of CSRC Think Tank members. The need for a final

FIGURE 4 Options for CV Event Collection in Clinical Trials of Novel Cancer Therapies



Selected options for ascertaining and categorizing cardiovascular events in trials of novel cancer therapies. Abbreviations as in Figures 1 and 2.

diagnosis to complement a reported cardiovascular symptom, clinical sign or abnormal cardiovascular biomarker is recognized. The CSRC Think Tank therefore recommends that when AEs are reported for symptoms, signs, laboratory abnormalities, or other abnormal investigations that constitute potential signals of important cardiac or cardiovascular toxicity, ascertainment and recording of the underlying etiology should be pursued. Further collaborative discussions with regulatory authorities and sponsors will be imperative for implementation. Careful monitoring of the impact of such changes is also recommended to ensure that they do not create ambiguity or over-diagnosis and reporting.

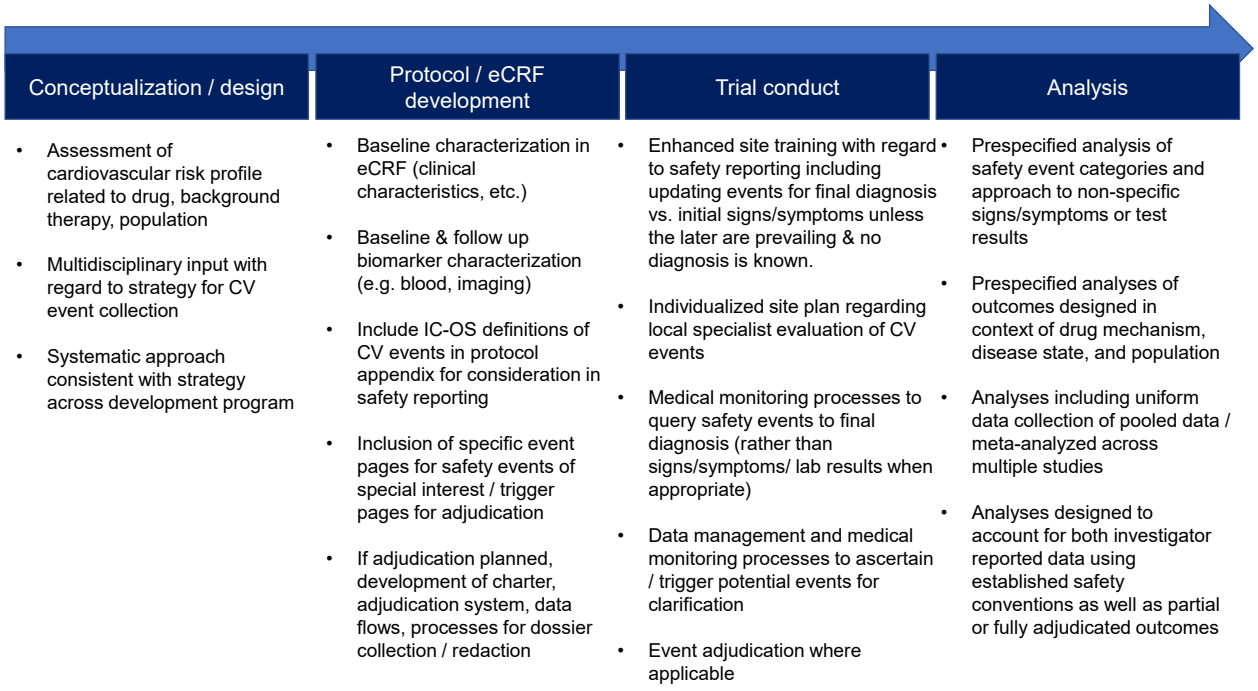
Ideally, the CTCAE grading system should be instructive to report the final diagnosis once known and remove the symptoms associated with the diagnosis. Physician researchers should support their staff in correct reporting of events and subsequent corrections. As most oncology trials are led by oncologists without specialist cardiovascular knowledge, careful engagement and education relating to potential cardiovascular events is paramount. The CTCAE terminology document and website contain helpful guidance, but reinforcement of this is recognized as a necessity. Contemporary clinical trial electronic data capture includes the possibility to trigger alerts and reminders, which could also be used to prompt trial staff to record diagnoses via CTCAE after initial reporting of symptoms or biomarker abnormalities. Future work will need to assess the role of artificial intelligence in the ascertainment and characterization of safety events in clinical trials.

AE ASSESSMENT IN TRIALS AND ROLE FOR ADJUDICATION

In addition to optimization of adverse event collection through CTCAE, additional specificity or characterization of predefined cardiovascular events may be desirable. For example, in cases of infrequent or complex diagnoses, such as myocarditis, collection of additional supporting information or formal adjudication may be useful to increase specificity.[31] Similarly, more frequent events (such as detection of asymptomatic myocardial injury through biomarker measurement) may benefit from additional data collection or adjudication to provide more specificity for diagnoses such as myocardial infarction.

CHALLENGES IN EVENT ASSESSMENT AND CATEGORIZATION. Challenges in evaluation and categorization of broad cardiovascular events include site education, site workload, costs associated with mandatory testing at baseline or in the context of a potential adverse event, and resourcing of formal adjudication work. In addition, whereas established and expected event definitions exist for a number of common cardiovascular events, established adjudication definitions for more rare events are lacking.[32,33] Due to these challenges, a strategic and

FIGURE 5 Considerations for Trial Design, Conduct, and Analysis



Considerations for trial design, conduct, and analysis to optimize cardiovascular event ascertainment and categorization. Abbreviations as in Figures 1 and 2.

collaborative approach is encouraged early in program development to ensure a systematic approach to event definitions, data collection in case report forms, and site training.

BASELINE CHARACTERIZATION AND DATA ACQUISITION. A critical aspect for consideration early in cancer therapy development is defining data to collect at baseline and throughout the study.[29] As investigators and sponsors consider what information will be critical to describe safety and the need for risk stratification for any safety signals observed, consideration should be given to whether baseline blood biomarkers, electrocardiograms, and imaging (eg, echocardiography) are necessary both to establish a baseline, and later for use in assessment and characterization of events during the course of the study.[34,35]

OPTIONS FOR CARDIOVASCULAR EVENT ASSESSMENT AND CATEGORIZATION. The optimal approach to cardiovascular event assessment and categorization in trials of cancer therapies will vary and may depend on factors such as drug mechanism of action, background therapies, population to be studied in terms of both cancer and cardiovascular risk, and phase of study (Table 1). Early phase studies may have relatively few events, and each safety event needs to be carefully scrutinized to allow the provision of granular outcome information. In later phase studies, there is usually a larger volume of data that requires aggregation for interpretation. Therefore the specificity of the "bins" used for event categorization becomes more essential at that stage. Factors that may favor traditional evaluation of safety data may include a mechanism of action with no known or suspected toxicity in a population and background treatments that are not associated with heightened cardiovascular risk or at early phases when events are expected to be rare. Factors that may favor enhanced approaches to event ascertainment and categorization may include mechanisms or targets of the cancer therapeutic under study with the potential to lead to adverse cardiovascular events, preclinical findings, or studies on top of background therapies or in populations associated with heightened cardiovascular risk.[36]

Selected options for event collection are outlined in Figure 4. Traditional collection of safety events using CTCAE is efficient across organ systems and broadly understood but may lack specificity for selected cardiovascular endpoints. Efforts in protocol development, site training, and site materials may

improve the systematic collection of events reported through CTCAE (Figure 5). For example, inclusion of case definitions for cardiovascular events in a protocol appendix may provide a reference for sites. In addition, sample cases during site training may provide enhanced education for site investigators and coordinators. Having an overarching plan for site based cardiovascular event assessment that is individualized depending on local resources and expertise at trial initiation may also help to improve specificity. Finally, systematic approaches through trial conduct including querying signs, symptoms, or isolated lab values until a final diagnosis is provided and aligned with protocol appendices and case definitions may assist in enhancing specificity.

Serious AE of special interest. If there are specific safety events for which additional data may be helpful for characterization, a subset of events designated as events of special interest are commonly defined for clinical trials. For these events, specific case report form pages may be created to capture additional data as reported by site investigators. Such data may be useful for ongoing medical monitoring, data management, and potentially for data safety monitoring committees. At study completion, the additional data may be utilized to provide more granular description of AE or provide structured data through consistent collection for exploratory analyses beyond data included in narrative fields. An example may be events of heart failure, where data regarding signs, symptoms, test results, and treatment provided in structured fields may provide greater characterization than event terms alone.

Event adjudication. Finally, adjudication of events using a formal committee, trained specialists, and review of redacted source documentation, and according to prespecified definitions is an established approach to event categorization in many cardiovascular trials. Such an approach provides the greatest consistency and specificity for event categorization; however, adjudication is resource intensive. Adjudication could be applied to a specific event type with challenging criteria for its ascertainment (eg, myocarditis) as triggered through an event of special interest page. Such an approach adds specificity but may suffer in sensitivity if potential events are reported using other event terms (eg, heart failure) through traditional safety forms. Broader cardiovascular adjudication may have the potential to increase sensitivity as well as differentiate AE of interest from more frequent background events or events potentially attributable to background therapies.

OVERALL, RECOMMENDATIONS FROM THE CSRC THINK TANK. These notably include redefining and revised grading of some of the cardiovascular events of the CTCAE and potential use of endpoint adjudication on the relevant subset of safety events and in specific situations. Other suggestions were made to better reinforce the strategic approach to cardiovascular event evaluation at the earliest possible time in a development program and to increase awareness of cardiovascular toxicities with early consultation with cardiology.

FUTURE DIRECTIONS AND ALIGNMENT WITH REGULATORY PERSPECTIVE

The first phase of the CSRC process to optimize cardiovascular event capture in cancer trials has been completed. Two further initiatives are necessary before the novel process can be finalized. These will be completed by 2 groups with a similar membership as the initial think tank, that is, clinicians (oncologists and cardiologists), pharmaceutical industry, and regulatory authority representatives.

GROUP 1: CTCAE GROUP. This group will focus on advising the CTCAE Governance Group in providing definitions more aligned to terms used in contemporary cardiology practice and grading in line with current management. Terms under revision include myocardial infarction, stroke, myocarditis, heart failure, thromboembolic events, and cardiovascular death. Definitions in the recent IC-OS document,[18] and the standardized cardiovascular adverse event definitions that are used in all clinical trials of cardiovascular drugs, will be used as reference.

GROUP 2: CANCER THERAPY TRIAL DESIGN WITH A FOCUS ON CARDIOVASCULAR EVENT COLLECTION. This group will focus on various aspects of all phases of trial design to ensure accurate cardiovascular adverse event ascertainment and classification. Many aspects of event capture will be considered but a recommendation for different methods for different trials is likely as a one-size-fits-all process is unlikely. Adjudication of AE will be discussed. Options for adjudication will vary from: 1) focused adjudication of events of special interest, to 2) adjudication of all potential cardiovascular events, to 3) no adjudication (reliance on investigator-reported events). It is likely that requirements for adjudication will depend upon many issues such as: drug class and mechanism, preclinical signals, cardiovascular risk of the population, phase of trial, and the active involvement (or not) of cardiology expertise at trial sites.

Identification of potential events will also be considered including the use of terms and investigator-reported events. Cardiovascular considerations in protocol development will be described while taking any related monitoring and economic issues into account. Recommendations of which cardiovascular events to report in each phase of development will also be discussed. Refinement of methods for ascertaining patient quality of life metrics and health economics in addition to cardiovascular safety will be key.

CONCLUSIONS

The aim of this collaborative effort is to fulfill the need for clear description of cancer treatment benefits alongside quantified cardiovascular AE. In addition, it is increasingly important that cancer therapy trials include patients at cardiovascular risk and promote the inclusion of patients from diverse racial and ethnic backgrounds. This is required so that findings can be applied to the broader population who may subsequently receive approved therapies.[3-5] A major step forward has been made with the acknowledgement of the importance of identifying and managing cardiotoxicity, including late effects, and the formation of an international collaborative group determined to optimize the capture of cardiovascular events in trials of new cancer therapies. Perhaps the most important advance has been the central role of the team responsible for the CTCAE process to consider redefining cardiac events and revising the grading of severity of cardiac events through the input of all stakeholders. The capture of cardiovascular events in cancer trials will not be via a "one-size-fits-all" method. Definitions of cardiovascular events are likely to be aligned but event adjudication will vary according to many different factors including study site cardiovascular expertise. The completion of this process requires consultation beyond the current think tank members before cementing the cardiovascular blueprint for the new era of clinical trials in oncology.

In summary, recommendations include:

- Refinement of the CTCAE definitions and grading
- Potential use of endpoint adjudication for relevant safety events
- Reinforcement of a recommended strategic approach to cardiovascular event ascertainment early in development programs as required per ICH guidelines with additional input from investigators, specialists, and regulatory authorities
- Careful consideration of baseline and serial tests for categorization in each study before initiation
- Continued and reinforced efforts in site training, study aids, protocol enhancements and ongoing medical monitoring and data collection to optimize safety collection and minimize variability
- Consideration of enhanced data collection through event of special interest pages
- Promotion of robust and active generation of post marketing clinical data to assess outcomes in practice

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APPENDIX For a supplemental table, please see the online version of this paper.

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