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ORIGINAL ARTICLE

Core outcome set for cardio-oncology: development of a set of outcomes for the cardiovascular assessment and monitoring of cancer patients and survivors

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Aims There is an increasing awareness of the evidence-based selection of outcomes to be measured in clinical trials and clinical practice. Currently, there is no core outcome set (COS) for cardio-oncology, which may hinder the (inter)national comparison of the effectiveness of research and the quality of cardio-oncology care. The aim of this study is to develop a standard and pragmatic patient-centred outcome set to assess and monitor cancer patients and survivors at risk of or with cardiovascular diseases.

Methods and results A list of outcome domains was generated through a review of registries and guidelines, and six patient interviews. The project team reviewed and refined the outcome domains prior to starting a two-round Delphi procedure conducted between January and June 2022. The panellists, including healthcare providers and researchers, were invited to rate the importance of the outcomes. Twenty-six experts from 11 countries rated a list of 93 outcomes (round 1) and 63 outcomes (round 2) to gain consensus on a list of outcome measures, and of demographic factors, health status, and treatment variables. The final COS includes 15 outcome measures, reflecting four core areas: life impact ($n = 2$), pathophysiological manifestations ($n = 9$), resource use/economic impact ($n = 1$), and mortality/survival ($n = 3$). Next, 6 demographic factors, 21 health status, 3 cardiovascular, and 9 cancer variables were included.

Conclusions This is the first international development of a COS for cardio-oncology. This set aims to facilitate (inter)national comparison in cardio-oncology care, using standardized parameters and meaningful patient-centred outcomes for research and quality of care assessments.

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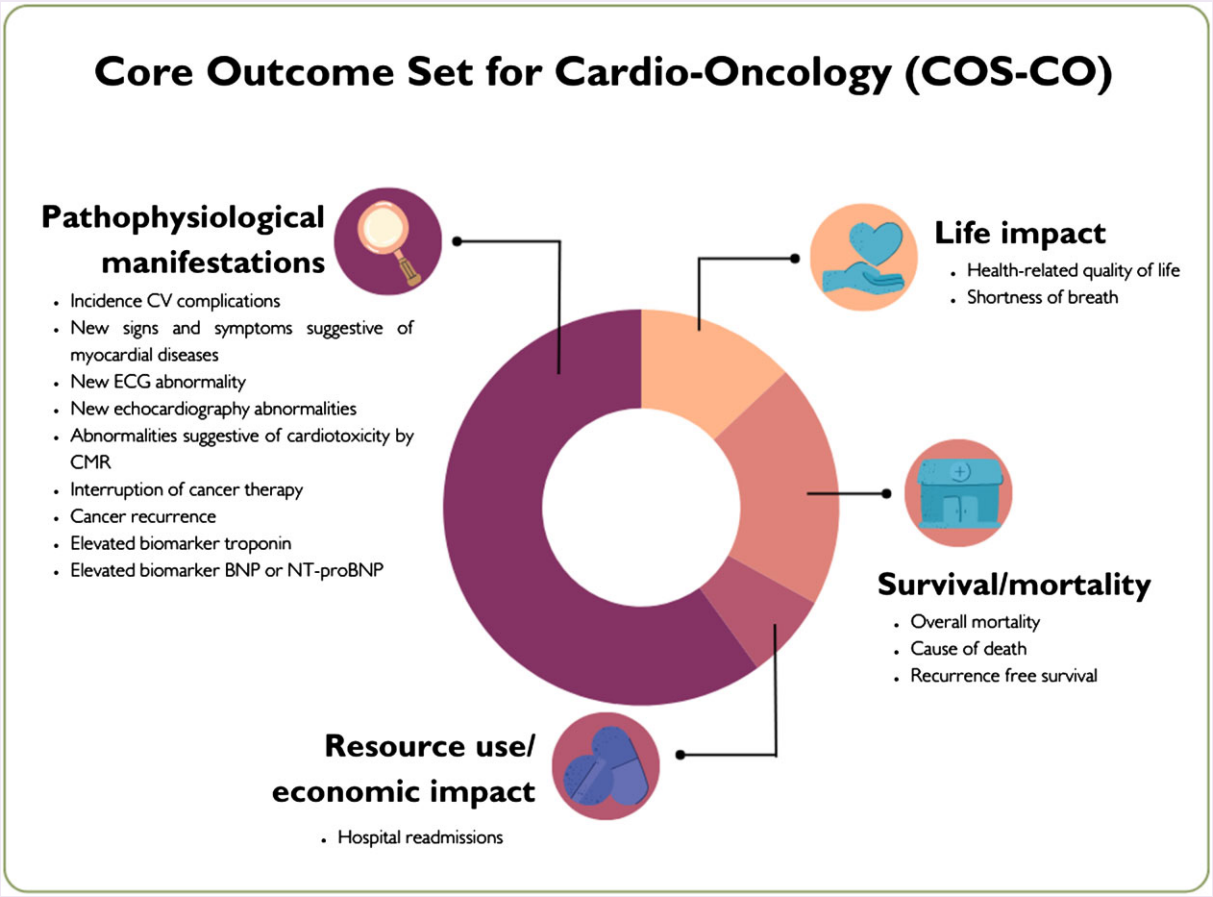
Graphical Abstract



Keywords Core outcome set • Cardio-oncology • Patient-reported outcomes • Patient registry • Outcome measure

Introduction

Advances in oncological therapies have improved the survival of cancer patients,[1,2] but short- and long-term adverse effects of anticancer treatments, especially in the cardiovascular system, can lead to premature morbidity and death among these cancer survivors.[3–5] Dedicated cardio-oncology clinics are being organized to provide multidisciplinary evaluation and care for the increasing number of patients presenting with cancer, cancer treatment, and associated cardiovascular diseases.[3,4,6,7] Although cardio-oncology is a fast-emerging field of research, the knowledge of many aspects of prevention, assessment, and long-term consequences is limited. One reason is the complexity and variation in cancer therapies and the related cancer therapy-related cardiovascular toxicity (CTR-CVT) as it depends on the type of drug used, combination with other drugs, dose, scheduling, route of administration, presence of cardiovascular risk factors, and comorbidities.[8,9] Second, the use of many different and heterogeneous outcome parameters in clinical studies and registries may hamper comparing data and pooling results of clinical trials to be used in evidence-based healthcare. Studies using (inter)national registries targeted both broad[10,11] and specific populations,[12–15] aiming to evaluate the prevalence,[14] the effectiveness of interventions,[12,13] the diagnostic value,[10,15] or daily practice,[11,15] using both retrospective[10,12,13] and prospective[11,14–16] data collection. Moreover, patient-reported outcome measures (PROMs) are not routinely used as key outcome measures, which limits the information of the impact of interventions in research and clinical practice.[17]

Therefore, a core outcome set (COS) for cardio-oncology (COS-CO) needs to be developed. A COS is a consensus-derived minimum set of outcomes to be assessed in clinical research and practice. The agreed standardized set of outcomes should be measured and reported in all trials for a specific clinical area. However, a COS does not limit researchers to choose additional outcomes and measurements.[18] Using identical outcomes across trials allows comparisons of results enhancing the value of evidence synthesis and reducing the risk of outcome reporting bias.[19,20] Moreover, the applications for the COS have been broadened to core information sets, the COS for routine care clinical practice, and patient registries.[20]

An increasing number of published and ongoing COS development studies are covering the areas of oncology[21] and cardiology.[22,23] Recent initiatives aimed to develop quality indicators and set up registries for the prevention, management, and monitoring of the CTR-CVT.[5,16,24] To date, there is no COS-CO developed. This COS-CO project is the first to develop a COS in the area of cardio-oncology. We used consensus methods to develop a standard, valid, and pragmatic patient-centred core set of outcome measures for the cardiovascular assessment and monitoring of cancer patients and survivors.

Key learning points

What is already known

- Cancer therapy-related cardiovascular toxicity impacts quality of life, morbidity, and death among cancer patients and survivors.
- In the fast-evolving field of cardio-oncology, the use of many different and heterogeneous outcome parameters across clinical studies and registries hampers data comparison and result pooling.
- The adoption of a core outcome set (COS), consisting of consensus-derived essential outcomes for assessment in both research and practice, facilitates standardized outcome measurement across trials, fosters evidence synthesis, and mitigates outcome reporting bias.

What this study adds

- The final COS for cardio-oncology includes 15 outcome measures, reflecting four core areas: pathophysiological manifestations, mortality/survival, life impact, and resource use/economic impact.
- The identification of baseline demographic, health status, and treatment variables alongside the minimum COS underscores the importance of comprehensive risk adjustment for accurately measuring cardio-oncology outcomes.
- This COS aims to facilitate (inter)national comparison in cardio-oncology research and care, using standardized parameters and meaningful patient-centred outcomes for research and quality of care assessments.

Scope of the core outcome set

The final core set will include outcome measures to be used for routine care and research. The target group consists of patients (1) who are at the start, undergoing, or have completed their oncological treatment program, (2) with (a high risk of) cardiovascular complications due to the cardiotoxicity of the oncological treatment, and/or (3) with pre-existing cardiac disease or existing cardiovascular risk factors such as diabetes mellitus, arterial hypertension, and smoking.

Methods

Study design

The project consisted of two phases: (1) a review and interviews with patients for identification of existing outcomes and (2) a consensus study using Delphi methods for the development of the COS-CO. The COS-STAndards for Development (COS-STAD) and the COS-STAndards for Reporting (COS-STAR) statement, to enhance reporting quality, were used to describe the development of a consensus-based set of core outcomes.[25,26] This study was registered in the COMET database (https://www.comet-initiative.org/Studies/Details/1956). The project team (PT) consisted of four people (B.M., K.V., B.V, B.C.) working in the field of cardio-oncology, cardiology, heart failure, trials, and nursing. They designed and co-ordinated the study. An overview of the COS development process is provided in *Figure 1*.

The study was conducted between January 2022 and June 2022 in two phases: (1) identification of existing outcomes and (2) a consensus study using Delphi methods.

Phase 1: identification of existing outcomes

Review of registries and guidelines

First, a list of outcomes was generated based on a review of existing registries and guidelines. The review was conducted to identify all possible outcomes, including rare endpoints and the patients' perspectives.[19] The search filter covered the concept of cardio-oncology broadly (synonyms, cancer- and heart-related terms) and was applied in the PubMed and Google Scholar databases. Next, authors were contacted to receive information about the outcomes used in the registries. There was no restriction about the year of publication. All outcomes were extracted by one author. The exact actual wording of each obtained outcome and, if possible, the definition of the outcome, was extracted in tables.

Patient interviews

Second, patients were invited for semi-structured interviews with the purpose of obtaining outcomes relevant for patients at risk of or with cardiovascular diseases before, during, and after oncological treatment. Patients were invited to participate if they were: Dutch speaking, aged 18 years or above, had a past or present oncological diagnosis, had an ongoing or completed oncological treatment such as chemotherapy and/or radiotherapy, were at risk for cardiovascular disease due to potential cardiotoxic treatment in the past or present, or had cardiovascular risk factors or cardiovascular disease (such as diabetes, hypertension, low left ventricle ejection fraction, and arrhythmias), and were willing and able to give informed consent. Patients were recruited at the cardio-oncology clinic (B.V.) and via oncology patient associations.

The interview guide, provided in Dutch, encompassed various aspects including participants' understanding of the research topic, their medical history, current challenges, priorities in cardiovascular care, and the impact of their condition on different facets of life. Specifically, participants were asked to articulate their perceptions on emotional, social, and financial impacts, physical symptoms such as pain and fatigue, as well as the influence of their condition on treatment and prognosis. Patients were asked questions to explore both positive and negative experiences across these domains. During the interview, responses were summarized to elucidate key themes and patients were encouraged to share any additional insights or perspectives they deemed relevant to the discussion. At the end of the interview, the drafted list of discussed problems, issues, and topics was checked with the patient. The interview was not recorded and hence not transcribed or coded.

Outcome classification

Each variable within the long list was labelled and divided into three sections: (1) baseline demographic and health status variables, (2) cardiovascular and cancer treatment variables, and (3) a list of outcome variables, which were classified into core areas and core domains.[27] Each section was reviewed by the PT who discussed outcomes addressing similar concepts and classified these using the International Consortium for Health Outcomes Measurement (ICHOM)[23] and Outcome Measures in Rheumatology (OMERACT) framework.[27] This resulted in a draft (1) list of demographic and health status variables, (2) list of treatment variables, and (3) core set of outcomes.

Phase 2: consensus study using Delphi methods

Participants

National and international experts were English-speaking healthcare providers [such as cardiologists, oncologists/haematologists, physiotherapists, dieticians (heart failure), nurses, and psychologists] or healthcare researchers. A total of 40 experts, identified through the network of the

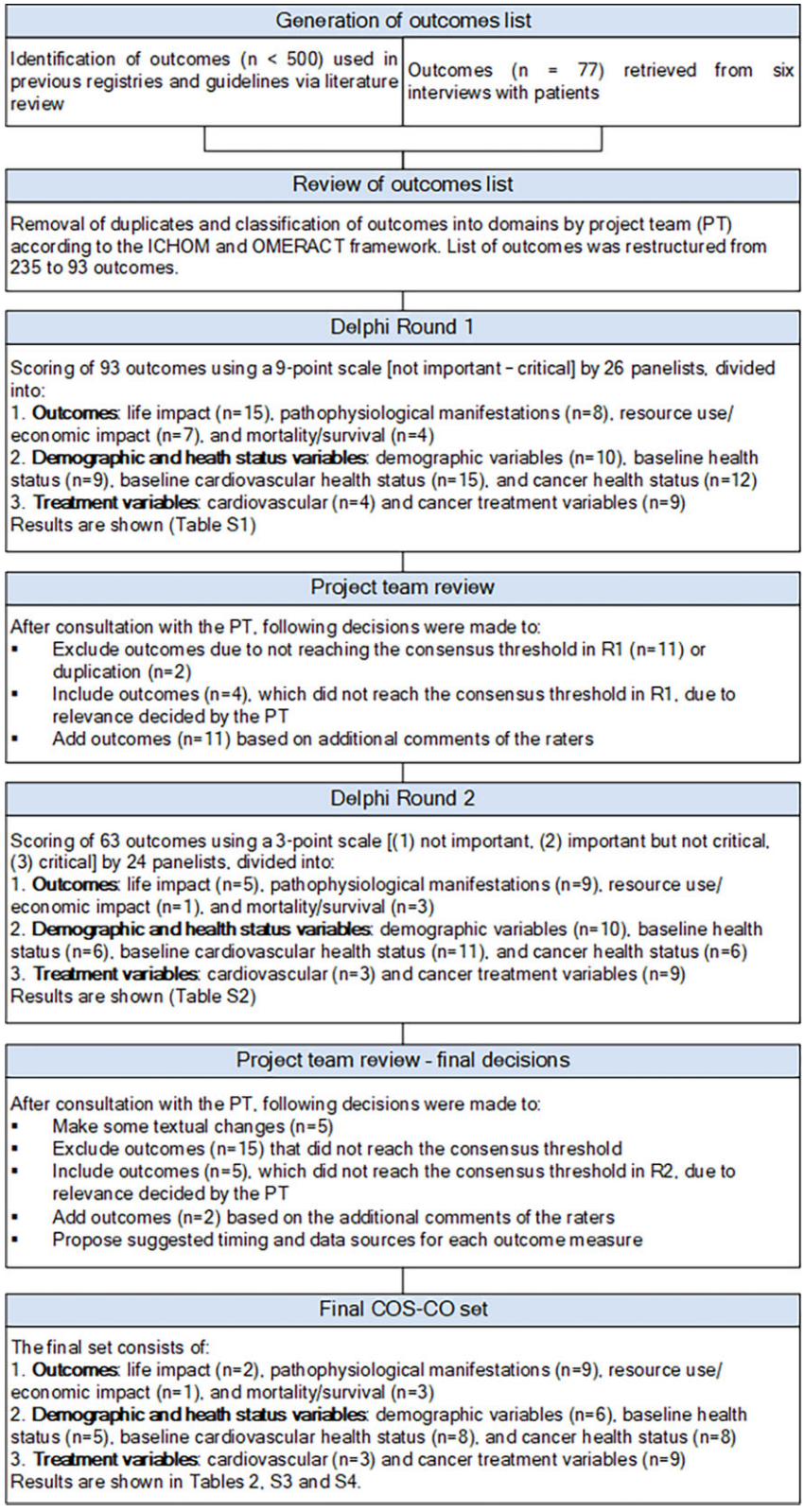


Figure 1 Development process of the core outcome set for cardio-oncology.

PT, were invited individually to participate. Additionally, an open invitation for participation was sent via the social media of the Association of Cardiovascular Nursing & Allied Professions, the COMET Initiative, and the Cardio-Oncology Council of the European Society of Cardiology (ESC).

Delphi procedure

The draft core set of outcomes was submitted to the experts using a Delphi procedure. The objective was to obtain consensus about the core set of outcomes by asking the experts to rate the relevance of each outcome. The draft core set of outcomes was presented to the experts via an online survey (Qualtrics). In this way, equal influence was given to all participants and individual participants being influenced by the opinions of any other participant were avoided.[28] At the start of the procedure, the experts were reminded of the importance of completing the procedure and anonymity was assured. An email reminder was sent to stimulate completion of the survey.

Delphi procedure round 1

The experts were emailed and asked to complete the online Delphi survey. Information about the study and how to complete the questionnaire was given. At the start of the survey, following data about the participants were collected: nationality, gender, age, educational background, work setting, specific (clinical) role, field of work, professional experience and previous participation in clinical trials, reviews, or publications in the area of cardio-oncology. Next, the experts were asked to judge whether each potential core outcome was important enough to be included in this COS-CO with a scoring system on a 9-point Likert scale from 1 'Not important for inclusion in COS-CO' to 9 'Critical, should be included in COS-CO'. If the experts could not rate the outcome because they did not know the outcome, the option 'I don't know the outcome' could be chosen. Consensus was set at 70% of the participants agreeing with a proposal, which means 70% scored an outcome critical for inclusion (7–9), excluding the option 'I don't know the outcome'.[19,20] Finally, the experts were given the opportunity to provide a rationale for their answers and add additional feedback, comments, and outcomes. After the first round, the PT discussed the results and made a proposal for round 2, taking into account the experts' additional feedback, comments, and outcomes.

Delphi procedure round 2

The experts who participated in round 1 were emailed and asked to complete the round 2 online Delphi survey. In the second round, the adapted core set of outcomes included the outcomes that obtained a consensus in the first round and additional outcomes suggested by the experts in round 1. The experts were asked to judge the proposal using a 3-point Likert scale of 1 'Not important enough to be considered in the COS-CO', 2 'Important but not critical to be considered for inclusion in the COS-CO', and 3 'Critical, should be included in the COS-CO'. Consensus was set at 70% of the participants agreeing with the proposal. The experts were also given the opportunity to add additional feedback and comments. After the second round, the PT discussed the results, additional feedback, and comments and made final decisions for the COS-CO.

Ethical approval

Research Ethics Committee approval was obtained by the Medical Ethics Committee of UZ Brussel/VUB (January 2022—BUN1432021000672). All participants received written information about the theoretical purposes of the study and how participation will strengthen clinical decision-making, contributing to patient-centred healthcare and improved methodology for cardio-oncology. Oral and written informed consent was obtained from all voluntary patients. Before completing the online Delphi survey, written informed consent was obtained from all experts. Participants' information was treated confidential and pseudonymized.

Results

Participants

Prior to the Delphi procedure, six patients were interviewed. Their median age was 62.5 [range 54–70] years and most of them were female ($n = 4$, 67%). They were diagnosed with Hodgkin's lymphoma ($n = 2$), non-Hodgkin's lymphoma ($n = 1$), breast cancer ($n = 3$), and/or chronic myeloid leukaemia ($n = 1$). One patient was receiving curative care, one patient was receiving palliative care, and four patients were in remission. All patients received an oncological treatment in the form of chemotherapy and/or radiotherapy.

In the first round of the Delphi procedure, 26 experts participated, of which 23 (88%) also participated in the second round. The experts who participated in the first round originated from 11 different countries and 20 (77%) experts were Europeans. Their median age was 44 [range 18–61] years, half were female, and a large group had a doctoral degree ($n = 17$, 65%). Most of them worked in a teaching/university hospital ($n = 21$, 81%) as a clinician (medical doctor or nurse) ($n = 20$, 77%) and/or as a clinical researcher ($n = 9$, 35%). The experts had a mean professional experience of 19 years in the domains of cardiology ($n = 26$, 100%), oncology ($n = 2$, 8%), nursing ($n = 5$, 19%), education/teaching ($n = 4$, 15%), and other domains. They were involved in different cardio-oncology research activities such as the cardio-oncology task force ($n = 15$, 58%), teaching/education ($n = 14$, 54%), clinical trials ($n = 11$, 42%), implementation research ($n = 9$, 35%), and quality improvement projects ($n = 9$, 35%). Half of them already published original research and 15% ($n = 4$) published a (systematic) review and/or meta-analyses in the field of cardio-oncology. An overview of the characteristics of the experts is provided in *Table 1*.

Item generation

The review of existing registries (>500 extracted outcomes) and six patient interviews (77 extracted outcomes) was conducted by one author (K.V.) generating a long list of outcomes. After labelling and removal of duplicates, the PT merged synonymous outcomes and classified according to the pre-agreed framework. Finally, a short list of 93 discrete outcomes were incorporated into an online questionnaire. First, demographic and health status variables were presented: demographic variables ($n = 10$), baseline health status ($n = 9$), baseline cardiovascular health status ($n = 15$), and cancer health status ($n = 12$). Second, treatment variables were presented: cardiovascular ($n = 4$) and cancer treatment variables ($n = 9$). Third, 34 outcomes divided into four core areas: pathophysiological manifestations ($n = 8$), mortality/survival ($n = 4$), life impact ($n = 15$), and resource use/economic impact ($n = 7$). The list used at the start of the Delphi study is presented in *Table S1* (Supplementary material online).

Delphi rounds

Delphi round 1

The 93 extracted outcomes were rated by 26 participants (Supplementary material online, *Table S1*). In total, 50 outcomes achieved a mean score of ≥7 by ≥70% of the participants, of which two were excluded due to duplication with other outcomes, which were rated higher [comorbidities Self-administered Comorbidity Questionnaire (SCQ) and overall survival (date of death)]. The outcome 'TNM-M tumour staging classification' was excluded due to not relevant since TNM-T and TNM-N were rated as not important for inclusion. Four outcomes did not reach the consensus threshold but were retained for round 2 after consultation with the PT: ethnicity, family history of premature cardiovascular disease, peripheral arterial disease risk, and electrolyte imbalance. Following free-text comments from participants, 11 new outcomes were added (Supplementary material online, *Table S2*).

Table 1 Characteristics of the experts (Delphi procedure)

n (%)	Participants R1 n = 26	Participants R2 n = 23
Country		
Australia	3 (11.5)	3 (13)
Belgium	9 (34.6)	8 (34.8)
Canada	1 (3.8)	1 (4.3)
Denmark	1 (3.8)	1 (4.3)
France	3 (11.5)	2 (8.7)
Italy	1 (3.8)	1 (4.3)
Netherlands	3 (11.5)	3 (13)
Poland	1 (3.8)	1 (4.3)
Spain	2 (7.7)	2 (8.7)
Ukraine	1 (3.8)	1 (4.3)
United Kingdom	1 (3.8)	1 (4.3)
Gender		
Female	13 (50)	12 (52.5)
Age		
Median [range] years	44 [18–61]	43 [18–61]
Education		
College degree	1 (3.8)	1 (4.3)
Bachelor degree	3 (11.5)	3 (13)
Master degree	5 (19.2)	5 (21.7)
Doctoral degree	17 (65.4)	14 (60.9)
Work setting[a]		
Local hospital	3 (11.5)	3 (13)
Teaching/university hospital	21 (80.8)	18 (78.3)
Nursing home	0	0
Community care	0	0
Education/university	3 (11.5)	3 (13)
Clinical research	0	0
Industry/commercial	0	0
Role[a]		
Clinician (nurse)	5 (19.2)	5 (21.7)
Clinician (medical doctor)	15 (57.7)	12 (52.2)
Clinician (other)	0	0
Clinical researchers	9 (34.6)	8 (34.8)
Educator	2 (7.7)	2 (8.7)
Research and development	1 (3.8)	1 (4.3)
Industry	0	0
Other	2 (7.7)	2 (8.7)
Field of work[a]		
General practice	1 (3.8)	1 (4.3)
Nursing	5 (19.2)	5 (21.7)
Cardiology	26 (100)	23 (100)
Oncology	2 (7.7)	2 (8.7)
Radiology—imaging	1 (3.8)	1 (4.3)
Psychology	0	0
Nutrition	0	0
Education/teaching	4 (15.4)	4 (17.4)
Methodology/statistics	2 (7.7)	2 (8.7)
Intensive care	1 (3.8)	1 (4.3)
Long-term care	0	0
Rehabilitation care	2 (7.7)	2 (8.7)
Other	3 (11.5)	3 (13)
Professional experience		
Median [range]	19 [2–40]	18 [2–40]
Cardio-oncology research activities[a]		
Clinical trial	11 (42.3)	9 (39.1)
Implementation research	9 (34.6)	7 (30.4)
Quality improvement project	9 (34.6)	8 (34.8)
Teaching/education	14 (53.8)	12 (52.2)
Cardio-oncology task force	15 (57.7)	12 (52.2)
Other	1 (3.8)	1 (4.3)
Cardio-oncology publication[a]		
Yes, original research	13 (50.0)	11 (47.8)
Yes, (systematic) review and/or meta-analyses	4 (15.4)	3 (13)
No	9 (34.6)	9 (39.1)

[a]Some experts selected more than one option resulting in totals exceeding the number of participants.

Delphi round 2

The 63 outcomes presented in round 2 were rated by 24 participants. In total, 47 outcomes achieved a mean score of ≥7 by ≥70% of participants (Supplementary material online, *Table S2*). Five outcomes did not reach the consensus threshold, but were included after decisions by the PT, due to administrative-relevant (referral reason CO clinic, data of inclusion), the international scope of the set (ethnicity), clinically relevant risk factors (family history of premature cardiovascular disease), and pragmatic reasons (Karnofsky score). Following free-text comments from participants, textual changes were made ($n = 5$), supporting information was added to one outcome (onset of new signs and symptoms suggestive of myocardial diseases), and two new outcomes within 'baseline cancer health status' were added for completeness reasons (previous hormonal therapy and previous targeted therapy).

Final set

The final COS includes 15 outcome measures, reflecting four core areas: pathophysiological manifestations ($n = 9$), mortality/survival ($n = 3$), life impact ($n = 2$), and resource use/economic impact ($n = 1$). Outcome measure definitions and sources are listed in *Table 2*.

In addition to defining the minimum COS, the panellists identified baseline demographic and health status, cardiovascular and cancer health status, and treatment variables, which are important to consider for risk adjustment when measuring cardio-oncology outcomes (see *Figure 2*). The set of demographic and health status variables includes demographic factors ($n = 6$), baseline health status ($n = 5$), baseline cardiovascular health status ($n = 8$), and cancer health status variables ($n = 8$) (Supplementary material online, *Table S3*). The set of treatment variables includes 12 outcomes divided into cardiovascular ($n = 3$) and cancer treatment variables ($n = 9$) (Supplementary material online, *Table S4*).

Table 2 Core outcome set for cardio-oncology

Patient population	Outcome domains	Measure	Suggested timing	Suggested data sources
Life impact				
All patients	Health-related quality of life	Tracked with the KCCQ-12	Tracked ongoing	Patient-reported
	Shortness of breath	NYHA class		
Pathophysiological manifestations				
All patients	Incidence cardiovascular complications	Major adverse cardiovascular events (MACE)	Tracked ongoing	Clinician-reported
	Onset of new signs and symptoms suggestive of myocardial diseases	List: shortness of breath, palpitations, vertigo (dizziness), orthostasis, chest pain, and peripheral oedema		
	New ECG abnormality	Normal, abnormal: repolarisation abnormality, conduction pathology, ACS, QT abnormality		
	New echocardiography abnormalities	LVEF, global longitudinal strain, LV ESD (mm), LV ESV (mL), LV EDV (mL), LV hypertrophy, E/A, deceleration time (ms), IVRT (ms), mitral e' average (cm/s), E/e', LA volume (mL/m^2), pseudonormal or restrictive pattern, mitral valve regurgitation, aortic valve regurgitation, aortic valve stenosis, tricuspid valve regurgitation, LVEF_3D, LV ESV (mL), LV EDV (mL)		
	Abnormalities suggestive of cardiotoxicity by CMR	Cardiac structure and function by CMR—used if other techniques are non-diagnostic or to confirm LV dysfunction if LVEF is borderline (detection of diffuse myocardial fibrosis using T1/T2 mapping and ECVF evaluation)		
	Interruption of cancer therapy	Yes or no, and reason		
	Cancer recurrence	Yes or no		
	Elevated biomarker troponin	Baseline troponin		
	Elevated biomarker BNP or NT-proBNP	Baseline BNP or NT-proBNP		
Resource use/economic impact				
All patients	Hospital readmissions	Number due to CV/cancer	Tracked ongoing	Clinician-reported
Survival/mortality				
All patients	Overall mortality	Date of death	Tracked ongoing	Administrative data
	Cause of death	Death attributed to cancer (specify) or cardiovascular death (specify)		Clinical
	Recurrence-free survival	Length of time after primary treatment to the time of recurrence or death		

CMR, cardiovascular magnetic resonance scan; ECG, electrocardiogram; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; BNP, B-type natriuretic peptide; E/A ratio, peak velocity blood flow from LV relaxation in early diastole (E wave) to peak velocity flow in late diastole caused by atrial contraction (A wave); ECVF, extracellular volume fraction; EDV, end-diastolic volume; E/e', index LV filling pressure; ESD, end-systolic dimension; ESV, end-systolic volume; IVRT, isovolumic relaxation time; LV, left ventricle; NT-proBNP, N-terminal pro b-type natriuretic peptide.

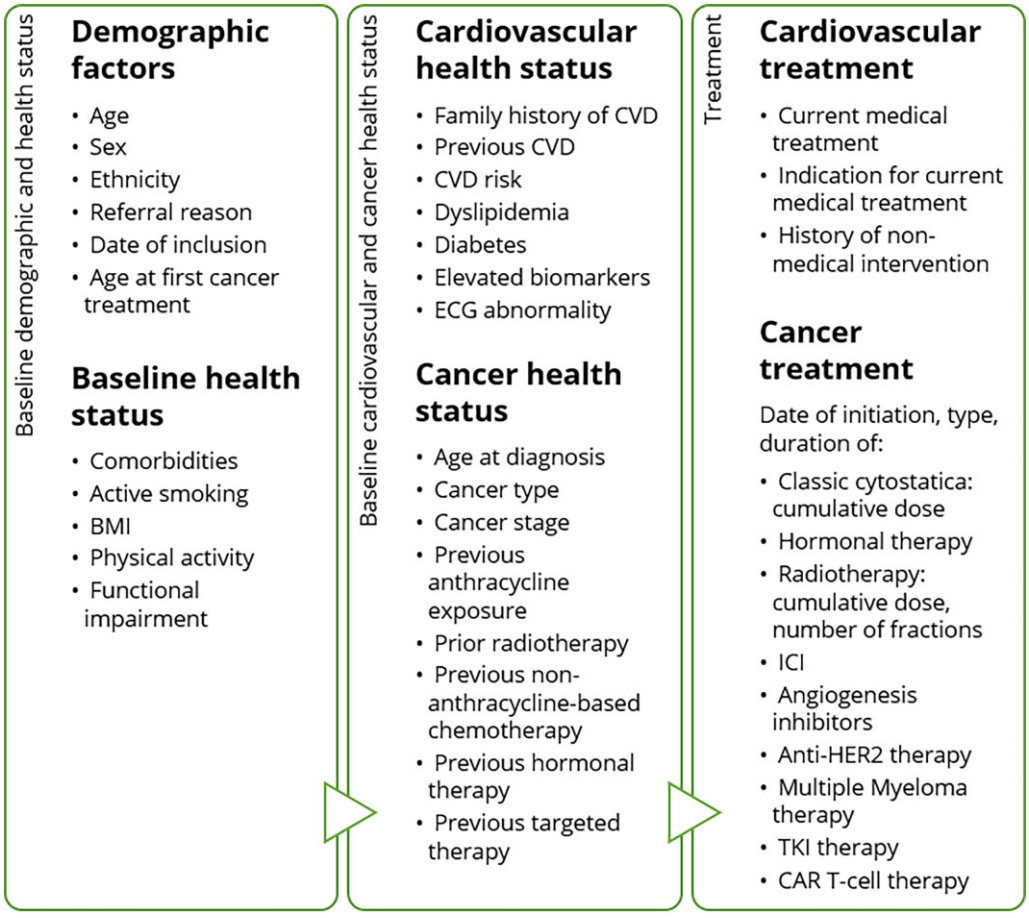


Figure 2 Demographic factors, health status, and treatment variables to be considered for risk adjustment when measuring cardio-oncology outcomes.

Discussion

This study presents the first COS for (1) the assessment of cardiovascular and cancer health status, and (2) the monitoring of life and economic impact, pathophysiological manifestations, and mortality of cancer patients and survivors with or at risk of cardiovascular diseases. The COS development process is based on the COMET methodology[11] using the ICHOM[23] and OMERACT[27] frameworks to classify the outcome measures.

The final COS consists of 15 outcome measures within four core areas. In addition to this COS, the study identified a minimum set of cardio-oncology-specific characteristics of the patient, health status, and treatment variables that are considered critical in the cardiovascular assessment and monitoring cancer patients and survivors.

Cardio-oncology is an emerging field, which is reflected in the rising number of published clinical trials, guidelines, and registries with the purpose to improve patients' outcomes via patient-centred and evidence-based prevention, monitoring, and treatment of cardiovascular complications.[29] To date, standardization of methods and outcome parameters in clinical trials and registries is lacking. Therefore, this COS-CO aims to facilitate (inter)national comparison in cardio-oncology research, using standardized parameters and meaningful patient-centred outcomes for research and quality of care assessments. The scope of this COS-CO reflects the breadth of this field as it applies to cancer patients (1) who are at the start, undergoing, or have completed their oncological treatment program, (2) with (a high risk of) CTR-CVT, and/or (3) with pre-existing cardiac disease or existing cardiovascular risk factors. As the use of this set is intended for routine care, registry, and research, it encompasses outcome measures and variables on demographic, baseline health status, and treatment. To assess and monitor the cancer patients using the COS-CO, data should be collected prospectively.

Measured outcomes and added value of patient-reported outcome measures

Pathophysiological manifestations are the most commonly measured outcomes today, which is also reflected in the results of this Delphi process. Outcome measures on cardiotoxicity were rated as highly relevant and include (1) incidence of cardiovascular complications defined as major adverse cardiovascular events, (2) onset of new signs and symptoms suggestive of myocardial diseases, (3) new ECG abnormality, (4) new echocardiography abnormalities, and (5) abnormalities suggestive of cardiotoxicity by cardiac magnetic resonance (CMR) imaging. The International Cardio-Oncology Society emphasizes the use of uniform definitions for cardiovascular toxicities of cancer therapies and to link these to outcomes in clinical practice and endpoints in clinical trials.[29] In accordance with the position paper on the role of serum biomarkers in cancer patients, two relevant biomarkers were included in the COS: elevated biomarkers troponin and B-type

natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP).[30] The proposed timelines, baseline (at first admission), yearly, or tracked ongoing, can change if clinically relevant as it depends on the type of cancer and therapy.[8]

Three mortality and survival outcome measures are included in the COS: overall mortality, cause of death (cancer or cardiovascular death), and the recurrence-free survival. The latter encompasses the length of time after primary treatment to the time of recurrence or death. Interestingly, within the field of oncology the emphasis is on survival, whilst within the field of cardiology, outcome measures on mortality are central. In this study, a combination of both was chosen.

While detection of cardiovascular complications and mortality is still the main endpoint in cardio-oncology care, monitoring PROMs, such as health-related quality of life (HRQoL), provides important insights into patients' own perspectives and can be used for comparing and monitoring quality of care.[31] Within our study, 2 out of 16 unique presented PROMs within the core area life impact did meet the criteria for inclusion: HRQoL tracked via the Kansas City Cardiomyopathy Questionnaire (KCCQ-12)[32] and shortness of breath using the New York Heart Association (NYHA) classification.[33] Although the KCCQ-12 and NYHA classification are well-known measures, the applicability and validity within the cardio-oncology population should be questioned as it is developed for heart failure patients. Interestingly, other PROMs such as overall well-being, depression, and fatigue were not considered critical for inclusion. One panellist commented that the questionnaires should be kept to an absolute minimum. This raises the question of feasibility, workload, and attitude of healthcare professionals towards PROMs. The composition of the expert panel, which consists mainly of healthcare professionals, could have had an impact on these results. Barriers and facilitators of routine PROM use in heart failure clinics have been identified.[34] However, a systematic review showed that PROMs have a more positive effect when feedback is provided to the patient and/or healthcare professional.[35] The importance of PROMs in cardiovascular clinical trials was already emphasized almost 10 years ago.[17] Future research into the validation and routine use of existing PROMs in cardiovascular clinical practice[31] and the development of new PROMs for the long-term follow-up of patients at risk or with cardiovascular diseases due to oncological treatment are needed.

Depending on specific clinical or research needs, the development of the COS with specific scopes will be relevant.

Resource use and economic impact

The OMERACT framework recommends including outcome domains within the area of resource use and economic impact. Resource use refers to the impact of health conditions both on society and on the individual, expressed as direct or indirect costs (e.g. productivity losses).[27]

In the COS-CO, the number of hospital readmissions was considered the most important cost to be included in the COS-CO by the panellists. To our knowledge, the economic impact of the CTR-CVT on individuals or society has been studied. The discussion of drug cost is the only reference within the new cardio-oncology guidelines.[8] Future research should focus on the economic burden of cardiovascular complications, both short- and long-term.

Cardio-oncology-specific characteristics

In addition to defining the minimum COS, this study identified cardio-oncology-specific characteristics, which are important to consider for risk adjustment when measuring cardio-oncology outcomes. Within the development of standard sets by the ICHOM initiative, this is defined as a list of case mix and treatment variables to provide a standardized terminology of treatment options over heterogeneous, international healthcare settings.[21,22] At present, risk factor models are developed but not encompassed in the present COS as it lacks validation.[36,37] Therefore, the separate risk factors were included within the COS-CO. The outcome measure body mass index (BMI) was rated as critical for inclusion, as it is the most frequently used tool for classifying patients within all healthcare settings across the world. However, it does not accurately reflect body adiposity nor prediction of the comorbidity risk of the patients. In the future, the use of other body composition measures, which are valid and feasible, should be considered in research and routine clinical practice.[38]

The result of a COS development process does not mean that the excluded outcome domains are not important or relevant in clinical cardio-oncological trials. A COS represents a minimum number of critical outcomes to be measured and reported in all trials in a specific area. Clinicians and researchers can elect additional outcomes if deemed relevant.[18] The COS-CO is intended as a feasible minimum set to be used in clinical practice, for registry and for research, which should be tested in the future.

The present COS-CO is in accordance with the recently published ESC cardio-oncology quality indicators for the prevention and management of the CTR-CVT in patients with cancer or cancer survivors.[24] These quality indicators encompass five domains: (1) structural framework, (2) baseline cardiovascular risk assessment, (3) CTR-CVT, (4) predictors of outcomes, and (5) the monitoring of cardiovascular complications during cancer therapy. The worldwide use of the COS-CO would also facilitate the data collection of these quality indicators.

The field of cardio-oncology is a fast-emerging field with a recent published global initiative, such as the G-COR registry published in 2023.[16] As the development and the incorporated outcome measures are not publicly available, no comparison can be made with the present COS-CO. Moreover, the feasibility of the registration, which will need a lot of resources, is yet to be determined.

Limitations

There are some limitations to this study. The generation of outcomes using review of registries was hampered by the lack of publicly available outcomes and outcome measurements. During the interviews with patients, it was often difficult for the patients to focus on their cardiovascular issues within their cancer treatment. Moreover, only six patients were interviewed and data saturation was not reached. The development is determined by expert opinion via the Delphi process, which reflects the views of the experts equally and independently. However, it has to be noted that the expert panel had mainly a background in cardiology, and not in oncology. This could have influenced the results (such as the wording of the outcomes) as oncologists play a role in the assessment of risk factors at the time of diagnosis—especially when there is no dedicated CO clinic within the hospital, in which the implementation of a database to provide outcome data is an important pillar.[9,39,40] Although the focus of this study was to provide a feasible minimum set of outcome measures, the feasibility of the COS-CO used for registry, clinical practice, and research is yet to be determined.

Conclusions

This set aims to facilitate (inter)national comparison in cardio-oncology care, using standardized parameters and meaningful patient-centred outcomes for research and quality of care assessments. The goal is to include sufficient detail to be meaningful while limiting the amount and complexity of collected data to ensure feasibility. Future research into the validation and routine use of PROMs within the cardio-oncologic field is required.

Supplementary material

Supplementary material is available at *European Heart Journal—Quality of Care and Clinical Outcomes* online.

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Data availability

The data underlying this article are available in the article and in its online supplementary material.

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