SUPPLEMENTAL MATERIAL

G-COR COMMITTEES. Appendix A

- **Executive Committee:**
- Responsible for running the global operation, coordination with all sites, recruitment and all operational tasks:
  A.J. Teske, R. Moudgil, D. Sadler, J Herrmann, A. Barac, A. Deswal.

- **Scientific committee:**
- Responsible for supervision of all content and scientific material, strict compliance with protocols, data quality, new projects, publications:
  A.J Teske, R. Moudgil, D. Sadler, A. Barac, A. Deswal, T. Neilan, J. Herrmann, S. Ganatra, P. Collier, C. Carvalho Silva, S. Makhoul, A. Ghosh, S. Szmit, T. Lopez, A. Sverdlov, Jun Chong, V. Agarwala, Z. Iakobishvili, P. Guerrero, EH Yang, H. Abdel Qadir, L. Zhang, J. DeCara, B. Bauer, D. Addison, N Akhter, R. Cheng, Vijay Rao.

- **Breast cancer:**
- A. Barac, H. Abdel Qadir, A. Daniele, MR DeTella, V Agarwala, R. C. Lenneman, B. Koczwara, V Zaha, R. Cheng, D. Cehic, S. Pauwaa, A Sverdlov.

- **Hematological malignancies:**
- A. Ghosh, A. Deswall, S. Ganatra, M. Fradley, J. Cautela, D. Gupta, D. Addison, J. DeCara.

- **Immune Check Point inhibitors:**
- S Ganatra, T. Neilan, L. Baldassarre, L. Zhang, V. Zaha, R., R. Moudgil, N. Palaskas, A. Barac, T Lopez.

- **Artificial Intelligence and informatics:**
- A. Guha, A. Asnani, A.J. Teske, N. Akhter.

- **Disparities in Cardio-Onc:**
- D. Sadler, N. Akhter, B. Bauer, L. Zhang, C. Lenneman. A. Arnold, J. DeCara, A. Asnani, A. Sverdlov, Abdel-Qadir, D. Addison, B.

- **Survivorship:**
- N. Bansal, J. Salas Segura, D. Gilon, A. Arnold, C. Zorkun, S. Pauwaa.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found

The Global Cardio Oncology Registry (G-COR). Registry design, primary objectives and future perspectives of a multi-center global initiative.

Background: Global collaboration in cardio-oncology (CO) is needed to understand the prevalence of cancer therapy related cardiovascular toxicity (CTR-CVT) in different risk groups, practice settings, and geographic locations. Furthermore, there are limited data on the socio-economic and racial/ethnic disparities that may impact access to care and outcomes.

Methods: We assembled cardiologists and oncologists from academic and community settings to collaborate in the first Global Cardio-Oncology Registry (G-COR). Subsequently, a survey for site resources, demographics, and intention to participate was conducted. We designed an online data platform to facilitate this global initiative.

Results: 119 sites responded to an online questionnaire on their practices and main goals of the registry: 49 US sites from 23 states and 70 international sites from 5 continents indicated a willingness to participate in G-COR. Sites were more commonly led by cardiologists and were more often university/teaching than community based. The average number of CO patients treated per month was 80±65/site. The top three G-COR priorities in CO care were breast cancer (BC), hematological malignancies (HM), and patients treated with immune checkpoint inhibitors (ICI). Executive and scientific committees as well as specific committees were established. A pilot phase for BC utilizing REDCap (Research Electronic Data Capture) Cloud platform recently started patient enrollment.

Conclusions: We present the structure for a global collaboration. Information derived from G-COR will help understand the risk factors impacting CTR-CVT in different geographic locations and therefore contribute to reduce access gaps in CO care. Risk calculators will be prospectively derived and validated.

Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported

Cardio-oncology has evolved from its infancy towards a mature and well-established subspecialty in the last decade. Multiple collaborative initiatives have been undertaken to move this field forward; the establishment of national and international cardio-oncology societies, the development of position papers(1,2), the launch of several peer

reviewed cardio-oncology journals(3), and recent international endeavors for board certification, just to name a few. Increased awareness in the cardiology, oncology, hematology, and radiotherapy communities, has sparked collaborations between different specialties to provide patient-tailored treatment options focused towards short- and long-term cardiovascular (CV) care and outcomes. Consequently, numerous academic and community hospitals have set up dedicated cardio-oncology clinics and programs to accommodate the growing need to serve this patient population.(4)

Cardio-oncology nevertheless remains a relatively new subspecialty addressing the CV care of cancer patients before, during, and after cancer treatment. Numerous cancer treatment modalities including cytotoxic and targeted chemotherapy, immunotherapy and radiation treatment can result in significant cancer treatment related cardiovascular toxicity (CTR-CVT).(5,6) Historically, cardiotoxicity referred to myocardial dysfunction and heart failure caused by systemic anticancer treatment. However, CTR-CVT comprises a very broad spectrum of CV disorders including systemic and pulmonary hypertension, arrhythmias, coronary artery disease, autonomic dysfunction, valvular dysfunction, and pericardial disease.(6,7) Novel treatments, such as immune checkpoint inhibitors (ICI), have revolutionised the therapeutic possibilities in patients with previously untreatable malignancies. With widespread implementation of these new drugs, previously unrecognised CV side effect such as ICI-associated myocarditis have emerged with potentially lethal outcome.(8) This echoes the unanticipated reports of heart failure after anthracyclines in the 1970s;(9) the excessive long-term morbidity and mortality from accelerated coronary and valvular heart disease after mantle field radiation in the 1980s;(10) and the unexpected high risk of left ventricular (LV) dysfunction and heart failure with trastuzumab in the 2000s.(11) This highlights the importance of continuous vigilance to monitor and investigate new anti-cancer drugs for their potential for CV toxicities, not only during the initial three phases of clinical drug trials but also after FDA approval when used on a larger scale. Post marketing surveillance is particularly relevant for identification of safety signals in patients that may have been excluded from clinical trials, such as those with pre-existing CV disease.

While several cardiovascular risk models are available for well-established cancer treatments, none have been thoroughly validated.(12) Consequently, identifying patients at high risk for CTR-CVT is challenging, hampering the development of robust practical guidelines for referral to cardio-oncology before the initiation of anti-cancer treatment. Moreover, most position papers and guidelines rely heavily on expert opinion regarding risk assessment, imaging, biomarkers selection, and duration and frequency needed for follow up assessments.(13) Discrepancies between the most recent American and European guidelines have recently been addressed with the hope of providing a roadmap for clinicians to use in their daily practice.(1) Also, the European Society of Cardiology (ESC), in conjunction with the Heart Failure Association (HFA) and the European Association of Cardiovascular Imaging (EACVI), proposed practical position statements on risk assessment and follow-up using imaging

and biomarkers.(14,15) However, it is unclear how such guidance translates to treating CTR-CVT to different practice settings, various regions of the world and in different socioeconomic and demographic groups.

A major limitation in various consensus opinions and guidelines is the lack of data due to a paucity of large-scale clinical trials upon which recommendations can be based in cardio-oncology. Additionally, most landmark pharmacologic or device interventional trials in cardiology excluded patients with active or recent cancer treatment and oncological trials in turn excluded patients with severe CV co-morbidities.(16) This mutual ostracizing of patient populations limits the translatability of cardiovascular guidelines in cancer patients and vice-versa. Only recently, several trials have emerged that are focused on treatment and/or prevention of CTR-CVT with variable success.(17–20) Currently, these trials lack sufficient power to change clinical practice due to discordant results, small sample sizes and heterogeneity in inclusion criteria or definitions of endpoints.(19) While awaiting more extensive prospective randomized clinical trials, real-world data obtained from our prospective multi-center, international registry will provide insight into optimal (or futile) screening and treatment strategies.(21,22)

Objectives	3	State specific objectives, including any prespecified hypotheses

1. To establish the incidence of CTR-CVT in patients referred to Cardio-Oncology services in all participating centers (university / community based)

2. To identify risk factors for CTR-CVT, derive and validate risk score models.

3. To evaluate geographic and regional differences in the use of biomarkers and imaging modalities, and their impact on the management of CTR-CVT.

4. To evaluate the impact of socioeconomic and demographic variables in access to care, surveillance strategies, treatments, and outcomes.

5. To describe outcomes of cancer survivors treated with different potentially "cardio-toxic" therapies in different geographic locations.

6. To provide a platform for multiple collaborations, sub-studies and prospective clinical trials.

7. To provide a Quality initiative (QI): sites can evaluate their data and compare it to the general database to identify opportunities for improvement of local practices.

Methods		
Study design	4	Present key elements of study design early in the paper
		Observational cohort study.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection

G-COR is a multi-center international observational cohort study that will prospectively enroll patients referred to dedicated cardio-oncology services. Medical centers (both academic and community) with dedicated cardio-oncology programs were invited to participate in this registry.

The principal investigator (PI) from each site will be responsible for data entry, data accuracy and follow-up of the enrolled patients. Data will be handled confidentially and coded. Patient privacy is protected by assigning a non-retraceable sequential subject number. Each participating center will have full access to its site`s data. Data will be collected in electronic case report forms (eCRF) on the REDCap Cloud server. The collected data will be stored in a central database, hosted by the Cleveland Clinic C5 Research Division, which also provides IT support, platform development, testing and validation, and security and data protection. Data management, RedCap Cloud platform implementation and Quality control by the C5 Research Division, and prospective data and global coordination for the global phase to be done by Cleveland Clinic Cardiovascular Outcomes Registries and Research team (CORR).

This electronic data capture (EDC) platform is a Cloud-based platform. It allows to store patient data per regional guidelines within multiple locations around the globe. Being a cloud-based platform, it allows the participating sites anywhere in the world to enter their data. The Registry is hosted and monitored by the Cleveland Clinic C5 Research Division and the Cardiovascular Outcomes Registries & Research (CORR) division. The Data Management (DM) group oversees database training, database-designed operating data dictionary (DDI), site activation, and queries for incomplete or out-of-range data. The REDcap Cloud is a secure validated platform, that was tested and validated for G-COR by the Cleveland Clinic DM team prior to the initiation of the Pilot phase. Prior to site activation, each site must obtain local Institutional Review Board (IRB) approval, execute a Data User Agreement (DUA), and must undergo protocol training monitored by the Executive Committee, and database training monitored by the DM team. After completion of training, database access is provided to trained healthcare providers as sites are activated.

The initial blueprint of the REDCap entry log was provided by the ONCOR registry investigators and adjusted and modified to meet the unique research questions of G-COR.(23) These platforms are designed to allow for data collection and storage in compliance with international regulations. This study was approved by the Cleveland Clinic Heart and Vascular Institute Research Committee and subsequently submitted and approved by the Cleveland Clinic Institutional Review Board (IRB).

The REDCap Cloud platform will be automated to detect incomplete, or out-of-range data, and investigators will be notified. The pilot phase with breast cancer patients started enrollment late in 2022 with up to 25 US centers projected to participate. This pilot phase is necessary to ensure that all the recruitment, legal agreements, DUA approvals, local IRB approvals, site activations, and data entry, are functioning well. In this phase, we are testing the sites' activation procedures, investigators' training, as well as the workflow of data entry into the eCRFs. The pilot phase has started with one

pillar, breast cancer, the most common condition at most surveyed institutions, and will confirm that all processes are in place. The G-COR Pilot phase has successfully started, and all the stated goals are being successfully achieved. Our goal is to have an efficient system in place to roll out the global phase. Twelve sites have already been activated and started recruitment at the time of this writing. Subsequently, with the lessons learned from the initial recruitment in the pilot phase, the G-COR international global phase will be launched subsequently.

Participating sites will prospectively enroll suitable patients. To avoid patient selection bias, sites will be instructed to enroll the first two eligible cardio-oncology consults every week in each pillar and subsequently consecutive patients. Each center will be allowed to establish an equivalent random mechanism that better fits their clinic schedule and patients' demographics. Data will be entered into eCRFs from patient interview and electronic health records of the clinical visits, according to current practice standards. Uniform data collection will be achieved by using a specially designed operating data dictionary (DDI) provided to each site at the time of activation which provides definitions of medical terms, definitions of specific parameters, and (ab)normal values. Each participating center is encouraged to comply with existing national/international recommendations, although patients will be managed at the discretion of the treating physician according to their usual standard of care and no intervention or change of treatment will occur related to G-COR.

Participants	6	*(a)*	*Cohort study* Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up

Patient recruitment and data collection will initially focus on breast cancer in the pilot phase of the study, followed by the three main pillars of this global registry based on the clinical priorities determined from a survey taken among the participating centers: 1) Cardio oncology in breast cancer (BC) patients, 2) hematological malignancies (HM) referred to cardio-oncology clinic, and 3) immune checkpoint inhibitor (ICI) with associated cardiovascular co-morbidities and/or complications. All variables collected will comply with General Data Protection Regulation (GDPR) guidelines.

Adult patients (18 years and older) with BC, HM, and patients treated with ICI, who present for their initial cardio-oncology consultation at participating sites will be eligible for enrollment and follow up provided that they are willing and able to provide written informed consent or conform to the local regulatory bodies guidelines for study participation enrollment.

Patients will have proposed clinical evaluations at baseline and at 3, 6, 9 and 12 months after enrollment, or as clinically necessary. Patients will have follow-up for 18 months after enrollment. The participating sites will have flexibility to follow their routine

		visits according to their clinical practice even if they don't strictly conform to the proposed visits timeline.
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
		At baseline, detailed information will be collected regarding: 1) demographic and socioeconomic variables, 2) cardiovascular risk factors and history including previous events, interventions and use of cardiovascular medications, 3) cancer information (e.g. TNM classification, receptor status in breast cancer patients, clinical-stage, etc.), 4) cancer treatment information (e.g. type, cumulative dose of chemotherapy, targeted therapy, immunotherapy, radiotherapy), 5) functional status (ECOG and the Karnofsky performance status)(24) , and 6) weekly exercise habits to evaluate its impact on cancer outcomes in different groups: exercise by time (< 30 minutes, 30-60, and >; 60) and times per week (0-1, 2 - 3, >4 times/week). New cardiovascular events or changes in cardiovascular medications, changes in cancer course or cancer treatment, along with vital signs, laboratory/biomarkers and echocardiographic imaging data will be prospectively collected during follow-up visits. G-COR will also collect results of additional non-routine, non-invasive testing such as Cardiovascular magnetic resonance (CMR), CT coronary angiography, CT coronary calcium score, Holter/event monitors, stress testing, SPECT, or MUGA scan, and invasive testing such as left and right heart catheterization and endomyocardial biopsy. Demographic data with age, sex, ethnicity, race, health insurance, employment status, geographical area (urban, suburban, rural), transportation, access to the internet and cell phone, and education history are collected. These social determinants of health are obtainable without IRBs and regulatory international entities (like GDPR) objections. Other variables, like Zip code (used for Social Vulnerability Index) are not collected due to conflict with de-identified data. The primary outcome will be the occurrence of CTR-CVT and overall outcome including cardiovascular and oncological death.(7) This will be correlated to (known and new) risk factors and risk groups, and the impact of the occurrence of cardiotoxicity on anticancer treatment and outcome. Furthermore, the multi-national, multicenter design of this registry offers the opportunity to study the prevalence and

		management of CTR-CVT in different practice settings and geographical locations as well as racial/ethnic disparities. Finally, socioeconomic determinants of access to care and outcomes will be assessed.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Registry design. Variables and definitions defined in a DDI (dictionary) provided to participants with all definitions. Data collection at each centger will reflect their standard of care
Bias	9	Describe any efforts to address potential sources of bias In low volume centers, all new cardio oncology consults with eligible patients will be enrolled to maintain the target enrolment numbers. In high volume centers, there will be a method (first two eligible patients of each week, or first two patients of a predetermined clinic or predetermined provider per week, in order to keep consistency in enrolment and to minimize inclusion bias.
Study size	10	Explain how the study size was arrived at: Registry target enrolment is based on the experience from G-COR Pilot, the realistic number of patients per week that can be enrolled per site, and the goal of diversifying the nature of participating centers from both academic and community practice settings to obtain representation from different geographic regions and countries.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why. Student T test for continuous variables will be utilized. All quantitative analysis will be done by designed statisticians that will have access to the RedCap Cloud database. Continues variables will likely include laboratory values, imaging measurements amongst others.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy As stated above a designated G-COR statistician will assist with all statistical analysis for this Registry and will address confounding factors, subgroups comparisons and interactions. Regarding missing data, the platform has a built-in feature that does not allow completion of any eCRFs with missing data. If data is unknown, it is checked as "unknown" but there are no blanks. In addition, the Data Management group from C5 Research team at Cleveland Clinic does queries for out of range values and contacts the

		sites. It has worked quite well in the pilot phase.
		(*e*) Describe any sensitivity analyses

Continued on next page

Results

Participants	13*	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed This is a study design paper. Results from the Registry are not yet available.
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	Give characteristics of the study participants (eg demographic, clinical, social) and information on exposures and potential confounders This is a study design paper. Results from the Registry are not available yet.
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure *N/A See above*
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period N/A: This is a study design paper. Results from the Registry are not available yet.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

Discussion

Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias G-COR has started the pilot phase and will need to secure additional funding for the global phase to provide long term sustainability. At the present time, funding applications are in progress to meet this need. Potential legal barriers for data sharing agreements at the international level. To address this

		issue, our legal team is working on solving compatibility of data sharing with different countries and compliance with GDPR. This global project includes more than one hundred institutions from 23 countries on 5 continents. The DUAs needed for each country/region are being evaluated and drafted by the Cleveland Clinic Legal Department. The compliance with GDPR for the European sites is addressed at multiple levels: a. All privacy issues and de-identified data are compliant with GDPR privacy protection rules. b. Compensations and liabilities are not in play since G-COR does not include any deviation from standard clinical care. c. GDPR has a provision allowing data sharing when it is in "important public interest". d. G-COR data are stored in the Cloud, not physically at any location. e. The Legal Department at the Cleveland Clinic is working on the requirements that will be in place for the DUAs (Data User Agreements) to be used with each specific country. Ensuring accuracy of data entry by different centers. The data management group will document training of each site prior to activation; has set up training videos, DDI dictionary, and online G-COR instruction and procedures manuals, and has alarms for out-of-range values and will review data in conjunction with executive committee to minimize/eliminate this challenge.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results Points 13-21: Not applicable to this Study Design paper. Results of G-COR are not yet available.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based The study design, teams and pilot study have been funded with internal funding by the Cleveland Clinic. A grant applications for G-COR has been submitted and currently under review.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.