Global Cardio Oncology Registry Protocol

Principal Investigator: Dr. Diego Sadler

Sponsor: Cleveland Clinic

Protocol Version: 1.0

Date: 20Jan2022

Protocol Synopsis

Title	Global Cardio Registry (G-COR)
Sponsor	Cleveland Clinic Division: Heart, Vascular and Thoracic Institute Department: Clinical Cardiology
Project Leadership	G-COR Executive and Scientific Committee
Principal Investigator	Dr. D. Sadler on behalf of the Executive and Scientific Committees
Rationale	The absence of a validated risk stratification model and an optimal treatment approach for cancer therapy-related cardiac dysfunction (CRTCD) in different patient populations limits the potential for effective screening and treatment strategies (10). Learning about these factors in a diverse patient population may provide insight on existing shortcomings in current practice and provide a blueprint to improve cardio-oncology care.
Registry Centers	Approximately 25 sites in the US will be involved in the pilot phase of the registry. Additional sites will be added following the pilot phase and the goal will be to expand to include approximately 118 sites from 23 countries.
Registry Objectives	1. Incidence of CTRCD in Cardio-Oncology services in all participating centers. 2. Identify risk factors resulting in increased CTRCD, and validate risk score models. 3. Evaluate geographic and regional differences in use of biomarkers and imaging modalities, and its impact of management of CTRCD. 4. Evaluate impact of socioeconomic and demographic variables in access to care, utilized surveillance strategies, treatments and outcomes. 5. Describe outcomes of cancer survivors treated with different potential “cardio-toxic” modalities in different geographic locations. 6. Provide a platform for multiple collaborations, sub-studies and prospective clinical studies.
Registry Design	Observational , prospective registry
Number of Subjects	Approximately 250 patients in the pilot phase of this registry
Target Population	Oncology patients presenting for cardio-oncology consultation. Patients participating in clinical trials where treatments are blinded will not be included.
Duration of Patient Participation and Duration of the Registry	18 months
Selection Criteria	1. In the pilot phase of the registry, only patients with: breast cancer will be entered. 2. Following completion of the initial pilot phase, , patients with the following cancers can be entered: a. Breast cancer b. Hematological malignancies (lymphomas, leukemia, multiple myeloma)

	c. Patients treated with immune check point inhibitors that present for cardio-oncology consultation.
Registry Visit Schedule and Assessments	Data collection time points at institutional standard of care visits.
Statistical Methodology	Multivariate analysis will be obtained for risk scores, and additional statistical analysis will be done according to enrollment data and sub-studies.

Principal Investigator Protocol Approval Page

Registry Title: Global Cardio Oncology Registry (G-COR)

Protocol Version: 1.0

Registry Sponsor: Cleveland Clinic

I, the undersigned, have read and approve this protocol and agree on its content. It is confirmed that the information and guidance given in this protocol complies with scientific principles, the guidelines of Good Clinical Practice.

Principal Investigator Signature:_____ Date: _____

Table of Contents

INTRODUCTION

1.1. Background Information

The field of cardio-oncology has grown impressively over the last decade. The increasing number of cancer survivors over this period of time has reached more than 16 million and is projected to be over 20 million over the next decade (1). This is in part a direct consequence of improvements in cancer therapy (2). This success is however mitigated by an increased risk of developing cardiovascular disease (CVD), a key determinant of increased morbidity and mortality in this population (3, 4). The association between CVD and cancer includes the existence of common risk factors, the increased incidence of CVD in cancer patients compared to non-cancer patients, and the now well established evidence of cancer treatment related cardiovascular disease (CTRCD) as a major factor in overall prognosis of cancer survivors (5,6).

Cardio-oncology is a new subspecialty addressing the cardiovascular care of cancer patients before, during, and after cancer treatment. Numerous treatment modalities commonly used for cancer treatment including agents used for chemotherapy, immunotherapy, and radiation treatment can result in significant CTRCD (7, 8). The early detection through the use of clinical evaluation, advanced imaging modalities, and biomarkers has the potential of allowing completion of cancer treatment while protecting cardiovascular health through close surveillance and potential cardio-protective strategies (9). There is a lack of data from large clinical trials in many of the commonly recommended practices in cardio-oncology (10, 11, 12). Furthermore, the impact of CTRCD in different practice settings, different parts of the world and in different socioeconomic and demographic groups is unknown

1.2. Registry Rationale

The absence of a validated risk stratification model and an optimal treatment approach for cancer therapy-related cardiac dysfunction in different patient populations limits the potential for cost-effective screening and treatment strategies (10). Learning about these factors in a diverse patient population may provide insight on existing shortcomings in current practice.

The Global Cardio-Oncology Registry (G-COR) is a multinational, multicentre prospective registry with the goal of obtaining clinical, laboratory, imaging, demographic, and socioeconomic data for cardio-oncology patients treated in different parts of the world both in large academic medical centres and in community hospitals, responsible for the care of a large number of these patients. The initial pilot phase of this registry will enroll patients from sites in the US.

The main objectives are to establish the incidence of CTRCD in different risk groups, in different practice settings, and diverse geographic locations, identify risk factors that can be prospectively used to establish and validate risk scores, and to determine the socioeconomic and demographic

factors that may impact access to care, (13-18) received treatments and outcomes in different countries.

The goal of this multinational collaboration is to provide a large database and platform for prospective sub-studies and eventually develop additional collaborations with a platform for clinical studies and trials following the initial pilot phase.

2. OBJECTIVES

1. Incidence of CTRCD in Cardio-Oncology services in all participating centers.
2. Identify risk factors resulting in increased CTRCD, and validate risk score models.
3. Evaluate geographic and regional differences in use of biomarkers and imaging modalities, and its impact of management of CTRCD.
4. Evaluate impact of socioeconomic and demographic variables in access to care, utilized surveillance strategies, treatments and outcomes.
5. Describe outcomes of cancer survivors treated with different potential "cardio-toxic" modalities in different geographic locations.
6. Provide a platform for multiple collaborations, sub-studies and prospective clinical studies.

3. REGISTRYREGISTRY DESIGN

Multicenter prospective observational cohort registry.

The Global Cardio-Oncology Registry (G-COR) is a multicenter observational cohort registry that will prospectively enroll patients evaluated in cardio-oncology services. Based on initial site feasibility outreach, three areas were identified as the main topics of interest at participating sites that will impact their practices. These three areas will be the three pillars of this Global Registry: 1. Breast cancer. 2. Hematological malignancies (Lymphomas, leukemia and Multiple Myeloma were identified as the three main hematological malignancies topics). 3. Immune check point inhibitors. These will be the three basic pillars for the G-COR protocol. The initial pilot registry will focus on patients with breast cancer, but the goal is to increase the number of pillars at a later time, incorporating other important areas of cardio-oncology.

Participating hospitals will enroll patients by entering information according to their current practice standards. In order to strengthen the data, we will encourage participating sites to follow a standardized approach with the goal of assessing patient treatments and outcomes under comparable conditions.

A standardized approach will be proposed: For the patients participating in this registry the following information will be collected, provided it is relevant to their clinical scenario and obtained following the local institution's standard of care:

- Clinical consultation (including BP measurement).
- ECG.
- Complete metabolic profile, hematological profile, blood glucose, lipid profile, and glomerular filtration rate calculation evaluated before initiation of treatment and periodically thereafter.
- Transthoracic echo (TTE) including LVEF measurements (2-dimensional Simpson biplane method, 3-D when available) and global longitudinal strain (GLS).
- Cardiac magnetic resonance (CMR) when available if the quality of TTE is suboptimal.
- Where possible in accordance with standard of care, the same imaging modality and same equipment/brand for longitudinal monitoring should be utilized.
  Management of modifiable cardiovascular risk factors and diseases
- Exercise and dietary habits.

Follow up assessments and evaluations will be collected per the local institutional standard of care. The participating sites will have flexibility to follow their routine visits according to necessity. Once the patient reaches the 18 month time point, this will conclude their participation in the registry. Patients will complete participation the registry by either reaching the last scheduled follow up visit, voluntary withdrawal of the registry, or death.

Table 1.1: Data Collection Time Points.

Procedure/Assessment	Baseline	Follow Up SOC Visits
Medical History & Demographics including Socioeconomic & Pregnancy	X	
Cardiac History (Cardiovascular risk factors and diseases.)	X	
Prior Malignancy	X	
Clinical Visit	X	X
Cardiovascular & Diabetic Medications	X	X
ECG	X	X
Echocardiogram (i.e. TEE, TTE, etc.) including LVEF measurements (2-dimensional Simpson biplane method, 3-D when available) and global longitudinal strain (GLS) (CRF captures many more data points)	X	X

Vital Signs (e.g. HR, Ht, Wt, BP, RR, SpO_2, Temperature, BMI)	X	X
Current Malignancy (i.e. Cancer stage, tumor type, receptors, metastatsis, radiation therapy) including all three pillars and cardiovascular events	X	X
Laboratory Data (CMP, hematological profile, blood glucose, lipid profile, glomerular filtration rate*)	X	X
Additional Investigations / Testing (e.g Cardiac magnetic resonance (CMR), SPECT / PET, MUGA, Stress ECHO & ECG, Genetic consueling, Holter Monitor, Coronary angiography, Neuro, etc.)	X	X
Stem Cell Transplantation	X	X
Treatment Log (Anthracyclines and Oncological Treatment Regimen)	X	X
Death		X
Exercise and healthy dietary habits	X	X

X= Should be collected if relevant to their clinical scenario at that visit and following the local institution's standard of care

*= Capture the laboratory tests that have been collected as SOC prior to initiation of treatment.

Platforms populated with clinical, laboratory, imaging, socioeconomic and demographic variables and data relevant to these patient populations will be utilized to prospectively collect information with the use of a REDCap Cloud eCRF. These platforms are designed to allow for data collection and storage in compliance with different international regulations.

3.1 Quality Initiative

G-COR will aim to provide bi-annual reports on key metrics to all participating centers for comparison with other geographic areas and the overall Registry as a quality initiative/feedback that will help to have an impact on standard of care treatments and outcomes. This will be implemented after the first 6-12 months of registry recruitment. Sites will have the opportunity to review their own data.

3.2 Governance

The governance of the G-COR will be supervised, guided and monitored by designated committees. These committees have been established with investigators from a variety of settings in order to represent the diverse nature of the participating institutions and the patients they serve, in order to be as inclusive as possible. This process will be described in each

committee's charter. Cleveland Clinic will serve as the coordinating center for the Registry and the C5Research will oversee data collection and data entry. Any data obtained from G-COR that will be utilized for future research projects at the Cleveland Clinic will be subject to IRB submission prior to initiation of a different/new research registry. Each participating site will submit to their local IRB for approval.

3.3 G-COR Committees

Executive Committee: Will oversee the structure, logistics, communications, sites activation, launching, progress, and overall conduction of the G-COR.

Scientific Committee: Will oversee the protocols, acquired data, adjustment/changes of protocols, data analysis, publications, authorships, new protocols, evaluation of proposed sub-studies or collaborations.

Breast Cancer Committee: Will examine variables, data analysis, publications, protocols, recommendations and analysis of G-COR on breast cancer patients.

Hematological Malignancies Committee: Will examine variables, data analysis, publications, protocols, recommendations and data analysis on G-COR hematological malignancies patients.

Immune Check Point Inhibitors Committee: Will examine variables, data analysis, publications, protocols, recommendations and data analysis on G-COR and data sets and clinical information to be obtained on patients treated with immune check point inhibitors.

Disparities in Cardio-Oncology Committee: Will oversee information obtained in socioeconomic, ethnicity and demographic data and make recommendations for this important aspect of all patients enrolled in G-COR.

Survivorship Committee: Will oversee the G-COR protocol for cancer survivor with focus in survivorship of young adults with history of childhood cancer.

Precision Medicine, Artificial Intelligence and Informatics Committee: Will evaluate data collection and explore protocols for use of AI, machine learning in G-COR and explore sub-studies and collaborations for use of AI in cardio-oncology in the global scale.

4. REGISTRY POPULATION

In the initial pilot phase, patients with breast cancer, who present for cardio-oncology consultation at participating sites will be eligible for enrollment and follow up. After the pilot phase, patients with hematological malignancies (lymphomas, leukemia, multiple myeloma), and patients treated with immune check point inhibitors will be included. Such patients will be eligible provided that are in compliance with all requirements from each local Institutional

Review Board (IRB) and are included as de-identified data to protect privacy as per protocol. The need for informed consent, according to the timing of data entry after the patient's visit will be established by each participating institutional IRB. Exclusion criteria will be unwillingness to provide written informed consent or waiver of informed consent depending on institutional requirements. Patients are free to withdraw from the registry at any time, for any reason, without prejudice to future care, and with no obligation to give the reason for withdrawal. The data obtained from a patient that withdraws from the registry will be kept in the registry and accounted for until the time of their registry withdrawal. Every patient will be given the opportunity to ask questions to the investigators before they decide whether they wish to participate in the registry.

Patients will be treated according to their standard of care and no intervention will occur related to G-COR. The main registry parameters and endpoints will be the occurrence of cardiovascular toxicity, the identification of risk factors and risk groups, and socioeconomic determinants of access to care and outcomes. Inclusion & Exclusion Criteria

Inclusion Criteria:

1. In the pilot phase of the study, only patients with breast cancer will be entered.
2. Patients that are of 18 years of age and older.
3. Following completion of the initial pilot phase, patients with the following cancers can be entered
    a. Breast cancer
    b. Hematological malignancies (lymphomas, leukemia, multiple myeloma)
    c. Patients treated with immune check point inhibitors that present for cardio-oncology consultation.
4. Patients are willing to follow up at the enrolling center.

Exclusion Criteria:

1. Unwillingness to provide written informed consent or waiver of consent depending on institutional requirements.
2. Patient will not be following up at the participating site.

5. DATA MANAGEMENT

The principal investigator (PI) from each site will be responsible for the accuracy of data collection and for follow up of the enrolled patients. All activated participating sites will have access to REDCap Cloud platform for data entry.

Data will be handled confidentially. Patient privacy is protected by assigning a non-retraceable sequential subject number.

Data will be collected in electronic case report forms (eCRF), through login on the REDCap Cloud server.

The collected data will be stored in a central database, which is hosted by the Cleveland Clinic C5Research Division. Please note no image files will be collected or stored as part of the registry.

Participating sites are expected to enter data within 5 business days of patient registry visits.

5.1 STATISTICAL ANALYSIS

The registry aims to collect a large cohort of patients from multiple institutions worldwide who have cancer and are at risk for CVD or have pre-existing CVD and those who develop CTRCD. Multivariate analysis will be obtained for risk scores, and additional statistical analysis will be done according to enrollment data and sub-studies. Data will be stored in a REDCap Cloud platform and statistical datasets will be obtained and analyzed.

6. ETHICAL CONSIDERATIONS

Internal Review Board/Ethics Committee approval will be obtained by each participating site. Participation in G-COR will not provide a direct benefit for the patients other than their contribution to the advancement of knowledge and science.

7. PUBLICATION POLICY

There will be strict control of research quality, integrity, individual merit and contributions to establish authors' priority order for publications to be determined by the scientific committee.

8. REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(1):7-30. doi:10.3322/caac.21590
2. de Moor JS, Mariotto AB, Parry C, et al. Cancer survivors in the United States: prevalence across the survivorship trajectory and implications for care. Cancer Epidemiol Biomarkers Prev. 2013; 22:561–70.
3. Verdecchia A, Francisci S, Brenner H, et al. Recent cancer survival in Europe: a 2000–02 period analysis of EUROCARE-4 data. Lancet Oncol. 2007; 8:784–96.
4. Daher IN, Daigle TR, Bhatia N, Durand J-B. The prevention of cardiovascular disease in cancer survivors. *Texas Hear Inst J*. 2012;39(2):190-198.
5. Oeffinger KC, Mertens AC, Sklar CA et al. Chronic health conditions in adult survivors

of childhood cancer. N Engl J Med 2006; 355:1572-82.

6. Miller KD, Siegel RL, Lin CC et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin 2016; 66:271-89.
7. Herrmann J. From trends to transformation: where cardio-oncology is to make a difference. *Eur Heart J*. 2019;40(48):3898-3900. doi:10.1093/eurheartj/ehz781
8. Sturgeon KM, Deng L, Bluethmann SM, et al. A population-based registry of cardiovascular disease mortality risk in US cancer patients. *Eur Heart J*. 2019;40(48):3889-3897. doi:10.1093/eurheartj/ehz766
9. Alexandre J, Cautela J, Ederhy S, et al. Cardiovascular Toxicity Related to Cancer Treatment: A Pragmatic Approach to the American and European Cardio-Oncology Guidelines. *J Am Heart Assoc*. 2020;9(18):e018403. doi:10.1161/JAHA.120.018403
10. Armenian SH, Lacchetti C, Barac A, et al. Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol Off J Am Soc Clin Oncol*. 2017;35(8):893-911. doi:10.1200/JCO.2016.70.5400
11. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (E. *Eur Heart J*. 2016;37(36):2768-2801. doi:10.1093/eurheartj/ehw211
12. Virani SA, Dent S, Brezden-Masley C, et al. Canadian Cardiovascular Society Guidelines for Evaluation and Management of Cardiovascular Complications of Cancer Therapy. *Can J Cardiol*. 2016;32(7):831-841. doi:10.1016/j.cjca.2016.02.078
13. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69(1):7-34. doi:https://doi.org/10.3322/caac.21551
14. Ward E, Jemal A, Cokkinides V, et al. Cancer disparities by race/ethnicity and socioeconomic status. *CA Cancer J Clin*. 2004;54(2):78-93. doi:10.3322/canjclin.54.2.78
15. Bach PB, Schrag D, Brawley OW, Galaznik A, Yakren S, Begg CB. Survival of blacks and whites after a cancer diagnosis. *J Am Med Assoc*. 2002;287(16):2106-2113. doi:10.1001/jama.287.16.2106
16. Bibbins-Domingo K, Pletcher MJ, Lin F, et al. Racial differences in incident heart failure among young adults. *N Engl J Med*. 2009;360(12):1179-1190. doi:10.1056/NEJMoa0807265
17. J. BE, J. BM, E. CS, et al. Heart Disease and Stroke Statistics—2017 Update: A Report From the American Heart Association. *Circulation*. 2017;135(10):e146-e603. doi:10.1161/CIR.0000000000000485
18. Van Dyke M, Greer S, Odom E. *Heart Disease Death Rates Among Blacks and Whites*

Aged ≥35 Years — United States, 1968–2015.; 2018. doi:http://dx.doi.org/10.15585/mmwr.ss6705a1

APPENDIX

Appendix I: Abbreviations

- BP: Blood Pressure
- CMR: Cardiac Magnetic Resonance
- CTRCD**:** Cancer Therapy-Related Cardiac Dysfunction
- CVD: Cardiovascular Diseases
- ECRF: Electronic Case Report Form
- GLS: Global Longitudinal Strain
- IRB: Institutional Review Board
- LVEF: Left Ventricular Ejection Fraction
- TEE: Transthoracic Echocardiogram