The Australia and New Zealand Cardio-Oncology Registry (ACOR): evaluation of chemotherapy-related cardiotoxicity in a national cohort of paediatric cancer patients

Daniel Lapirow[3], Andre La Gerche[3,7], Claudia Toro[2], Emma Masango[1], Ben Costello[7], Enzo Porello[1,5], Louise Ludlow[1,2], Glenn Marshall[9], Toby Trahair[9], Marion Mateos[8,9], Jeremy Lewin[11], Jennifer Byrne[11,12], Rose Boutros[11], Rebecca Manudhane[13], John Heath[14], Julian Ayer[11], Melissa Gabriel[11], Thomas Walwyn[15], Jelena Saundankar[15], Jonathon Forsey[8,11], Ha Le[1,16], Kylie Mason[10,17], David Celermajer[18,19], Peter Downie[20], Roderick Walker[21], Lucy Holland[21], Michelle Martin[2], Lorna McLeman[2], Yonatan Diamond[2], Maurizio Marcocci[22,23], Susan Donath[1], Michael Cheung[1,6], David A. Elliott[1,2,4]* and Rachel Conyers[1,2,3]*

*contributed equally

[1] Murdoch Children's Research Institute, The Royal Children's Hospital, 50 Flemington Road, Parkville, VIC 3052, Australia

[2] Children's Cancer Centre, The Royal Children's Hospital, 50 Flemington Road, Parkville, VIC 3052, Australia

[3] Medicine, Dentistry and Health Sciences, The University of Melbourne, Grattan Street, Parkville, VIC 3010, Australia

[4] Department of Paediatrics, The University of Melbourne, Grattan Street, Parkville, VIC 3010, Australia

[5] Department of Physiology, The University of Melbourne, Grattan Street, Parkville, VIC 3010, Australia

[6] Department of Cardiology, The Royal Children's Hospital, 50 Flemington Road, Parkville, VIC 3052, Australia

[7] Baker Heart and Diabetes Institute, 75 Commercial Road, Melbourne, Victoria 3004, Australia

[8] Sydney Children's Hospital Randwick, High St, Randwick, NSW 2031, Australia

[9] University of New South Wales, High St, Kensington, NSW 2052, Australia

[10] Peter MacCallum Cancer Centre, 305 Grattan Street, Melbourne, VIC 3004, Australia

[11] The Children's Hospital at Westmead, Corner Hawkesbury Road and Hainsworth Street, Westmead 2145, Australia

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/imj.14719

[12] Discipline of Child and Adolescent Health, The University of Sydney, The Children's Hospital at Westmead, Corner Hawkesbury Road and Hainsworth Street, Westmead 2145, Australia

[13] The Michael Rice Centre, Women's and Children's Hospital, 72 King William Road, North Adelaide, SA 5006, Australia

[14] Paediatric Oncology, Royal Hobart Hospital, 48 Liverpool Street, Hobart, TAS 7000, Australia

[15] Perth Children's Hospital, 15 Hospital Avenue, Nedlands, WA 6009, Australia

[16] School of Health and Soc. Dev, Deakin University, 221 Burwood Highway Burwood VIC 3125, Australia

[17] Clinical Haematology and Bone Marrow Transplant Service, The Royal Melbourne Hospital, 300 Grattan Street (corner of Royal Parade), Parkville, VIC 3050, Australia

[18] Cardiology Department, The Royal Prince Alfred Hospital, Level 11, KGV Building Missenden Road, Camperdown, NSW 2050, Australia

[19] Faculty of Health and Medicine, The University of Sydney, NSW, Australia

[20] Children's Cancer Centre, Monash Health, Monash Children's Hospital, 246 Clayton Road, Clayton , VIC 3168, Australia

[21] Queensland Children's Hospital, 501 Stanley St, South Brisbane, QLD 410, Australia

[22] University Food Group, 64-90 Sutton St, North Melbourne, VIC 3051, Australia

[23] My Room Children's Cancer Charity, 64-90 Sutton St, North Melbourne, VIC 3051, Australia

Abstract

Cancer therapy related cardiac dysfunction (CTRCD) is an area of increasing focus, particularly during the survivorship period, for paediatric, adolescent and adult cancer survivors. With the advent of immunotherapy and targeted therapy, there is a new set of mechanisms from which paediatric and young adult patients with cancer may suffer cardiovascular injury. Furthermore, cardiovascular disease is the leading cause of morbidity and mortality in the survivorship period. The recently established Australian Cardio-Oncology Registry (ACOR) is the largest and only population-based cardiotoxicity database of paediatric and adolescent and young adult (AYA) oncology patients in the world, and the first paediatric registry that will document cardiotoxicity caused by chemotherapy and novel targeted therapies using a prospective approach. The database is designed for comprehensive data collection and evaluation of the Australian practice in terms of diagnosis and management of CTRCD. Using the ACOR registry critical clinical information will be collected regarding predisposing factors for the development of CTRCD, the rate of subclinical LV dysfunction and transition to overt heart failure, further research into protectant molecules against cardiac dysfunction and aid in the discovery of which genetic variants predispose to CTRCD. A health economic arm of the study will assess the cost/benefit of both the registry and cardio-oncology clinical implementation. Finally, an imaging arm will establish if exercise magnetic resonance imaging (CMR) and VO_2 max testing is a more sensitive predictor of cardiac reserve in paediatric and AYA oncology patients exposed to cardiac toxic therapies.

INTRODUCTION

In recent decades, dramatic improvements in the treatment of childhood cancer have resulted in five-year survival rates of approximately 80%. However, a number of the antineoplastic agents responsible for these outcomes have cardiotoxic effects which have contributed significantly to morbidity and mortality among childhood cancer survivors.(1) The best known contributor to cardiotoxicity are the anthracyclines, a class of chemotherapeutic agents used extensively across both haematological malignancies and solid tumours. Anthracycline use is associated with cardiac complications ranging from sub-clinical echocardiographic abnormalities such as reduced left ventricular ejection fraction (LVEF), to overt heart failure, estimated to occur in up to 57%(2) of children treated with these agents. Anthracycline cardiotoxicity (ACT) is classified based on its temporal relationship to anthracycline therapy.(1) Acute-onset ACT occurs within a week of therapy initiation and is typically a transient phenomenon characterised by a pericarditis-myocarditis syndrome, arrhythmias, and depressed left ventricular contractility. (3) Early- and late-onset ACT occur within and after one year of therapy, respectively, and manifest with a progressive dilated cardiomyopathy.(1)

Risk factors for ACT in children include higher cumulative anthracycline dosage, concomitant mediastinal radiotherapy, as well as patient-specific factors such as female sex and younger age at diagnosis.(1, 3) Nevertheless, there is a high degree of intra-individual variability and unpredictability associated with ACT suggesting that a genetic component underlies this adverse drug reaction. Indeed, preliminary pharmacogenomic studies have revealed an association between ACT and a multitude of genetic polymorphisms associated with anthracycline cardiac functional pathways and hepatic clearance.(4-8).

Beyond anthracyclines, cancer therapeutic-related cardiac dysfunction (CTRCD) extends to a number of contemporary targeted therapeutics in both the adult and paediatric population. In breast cancer, the human epidermal growth factor receptor 2 (HER2) monoclonal antibody trastuzumab results in heart failure and treatment-limiting decreases in LVEF in 4% and 14% of patients, respectively,(9) and when combined with chemotherapy, significantly increases the risk of these outcomes compared with chemotherapy alone.(10) A recent meta-analysis revealed a dose-dependent increase in the risk of ischaemic heart disease among patients treated with the vascular endothelial growth factor (VEGF) inhibitor bevacizumab.(11) Furthermore, the multi-target tyrosine kinase inhibitor (TKI) sunitinib has been associated with left ventricular systolic and diastolic dysfunction, as well as clinical heart failure.(12, 13) The cardiotoxicity of this class, however, is less well-characterised compared with anthracyclines or trastuzumab.(14)

With 5-year survival rates of approximately 80% in paediatric cancer,(15) the monitoring and treatment of long-term therapy-related side effects including CTRCD have become paramount to the ongoing care of childhood cancer survivors. It is therefore important that a variety of cardiac investigations be evaluated in the assessment of CTRCD, and that the cost-effectiveness of interventions offered to patients with this complication be analysed. However, prospective studies of children exposed to cardiotoxic cancer therapy have yet to be conducted in Australia, and there are no standard predictors of cardiotoxicity that can be used for pre-treatment risk stratification or individualised dose titration.

Rationale for the Australian Cardio-Oncology Registry (ACOR)

ACOR is the largest and only population-based cardiotoxicity database of paediatric and adolescent and young adult (AYA) oncology patients in the world, and the first paediatric registry that will document cardiotoxicity in response to both chemotherapy and novel targeted therapies using a prospective and longitudinal approach.

To date, the systematic reporting and recording of CTRCD in paediatric patients has been sub-optimal.(16) The rate, clinical significance, evolution, and persistence of sub-clinical reductions in LVEF have not systematically documented. While monitoring cardiac function before, during, and after therapy helps physicians to identify these LVEF changes, the absence of clear paediatric guidelines means that follow-up and management of these patients varies widely, particularly in the early phase of LV dysfunction. Moreover, there is limited data on the incidence, management, and monitoring of cardiac dysfunction resulting from exposure to novel therapeutics. Recently, in the United States, Canada and Europe, cardio-oncology clinics have emerged with the intent to harmonise and coordinate approaches to CTRCD.(17) To date, no such public clinics exist in Australia.

The Australia Cardio-Oncology Registry (ACOR) is a repository for demographic and clinical data for all paediatric and AYA patients exposed to cardiotoxic cancer therapy across Australia and New Zealand. ACOR will prospectively compile a detailed data set that can be used to document cardiotoxicity (and other adverse outcomes) within paediatric, and AYA patients in order to inform guidelines and policy. This first of its kind cardio oncology biobank will

facilitate both genetic and mechanistic studies into the molecular pathogenesis of CTCRD. Thus, ACOR will provide a comprehensive longitudinal analysis of CTRCD in the paediatric and AYA cohorts, and facilitate ongoing research and discovery in primary and secondary prevention of cardiovascular complications arising from cancer therapy.

Objectives

ACOR is a unique initiative to improve the cardiovascular health of paediatric and AYA cancer survivors. The specific objectives are:

1: To expand Australia's first national cardio-oncology registry and biobank for paediatric and young adult oncology patients in order to assess the long-term management of chemotherapy related cardiomyopathy and characterise the progression as well as other clinical outcomes, including mortality and morbidity.

2: To develop and implement national cardio-oncology guidelines and clinics, for the identification and management of cardiovascular disease in paediatric and AYA cancer survivors.

3: To provide a comprehensive health economic data outlining (a) the cost and (b) the short-term cost-effectiveness of the both the registry and newly established cardio-oncology clinics to inform policy decisions by Government and private health providers.

4: To establish if modern imaging with exercise magnetic resonance imaging (CMR), VO_2 max testing is a more sensitive predictor of cardiac reserve in patients with and without ACT.

Partners

ACOR is a partnership including tertiary paediatric oncology and adult Oncology/Haematology institutes nationally including: The Royal Children's Hospital Melbourne, Monash Medical Centre Melbourne, Peter MacCallum Cancer Centre Melbourne, The Royal Melbourne Hospital, The Children's Hospital at Westmead, The Children's Hospital at Randwick, Hunter New England Health Newcastle, Queensland Children's Hospital, , Perth

Children's Hospital, Royal Hobart Hospital, The Women's and Children's Hospital South Australia and Starship Hospital New Zealand.

Eligibility

All paediatric and young adult patients (aged 0-35 years) with a new cancer diagnosis who have been exposed to cardiotoxic agents will be eligible to participate. Moreover, patients from this age group who have been treated for cancer within the preceding 5 years with known CTRCD will be eligible for inclusion. Agents considered to be cardiotoxic will include, but are not limited to; the anthracyclines daunorubicin, doxorubicin, doxorubicin liposome injection, epirubicin, idarubicin, and valrubicin, along with targeted therapies including trastuzumab, bevacizumab, lapatinib, sunitinib, sorafenib, and imatinib.

Patients with a prior diagnosis of congenital heart disease, pre-existing cardiomyopathy or Trisomy 21 will be excluded from the registry, along with those receiving palliative care at the time of recruitment. Further exclusion criteria include the absence of a legally acceptable representative capable of completing the informed consent document on behalf of those participants less than 18 years of age, and those who are unable to attend an appropriate institute for cardiac assessment.

Data Collection

Patients recruited into ACOR will be asked to consent to enrolment into four interlinked arms (Figure 1): (a) Registry;(b) Biobanking; (c) Extended Cardiac Evaluation; (d) Health Economic Analysis. The ACOR REDCap database records 300 clinical endpoints in a systematic manner across all participating institutes.

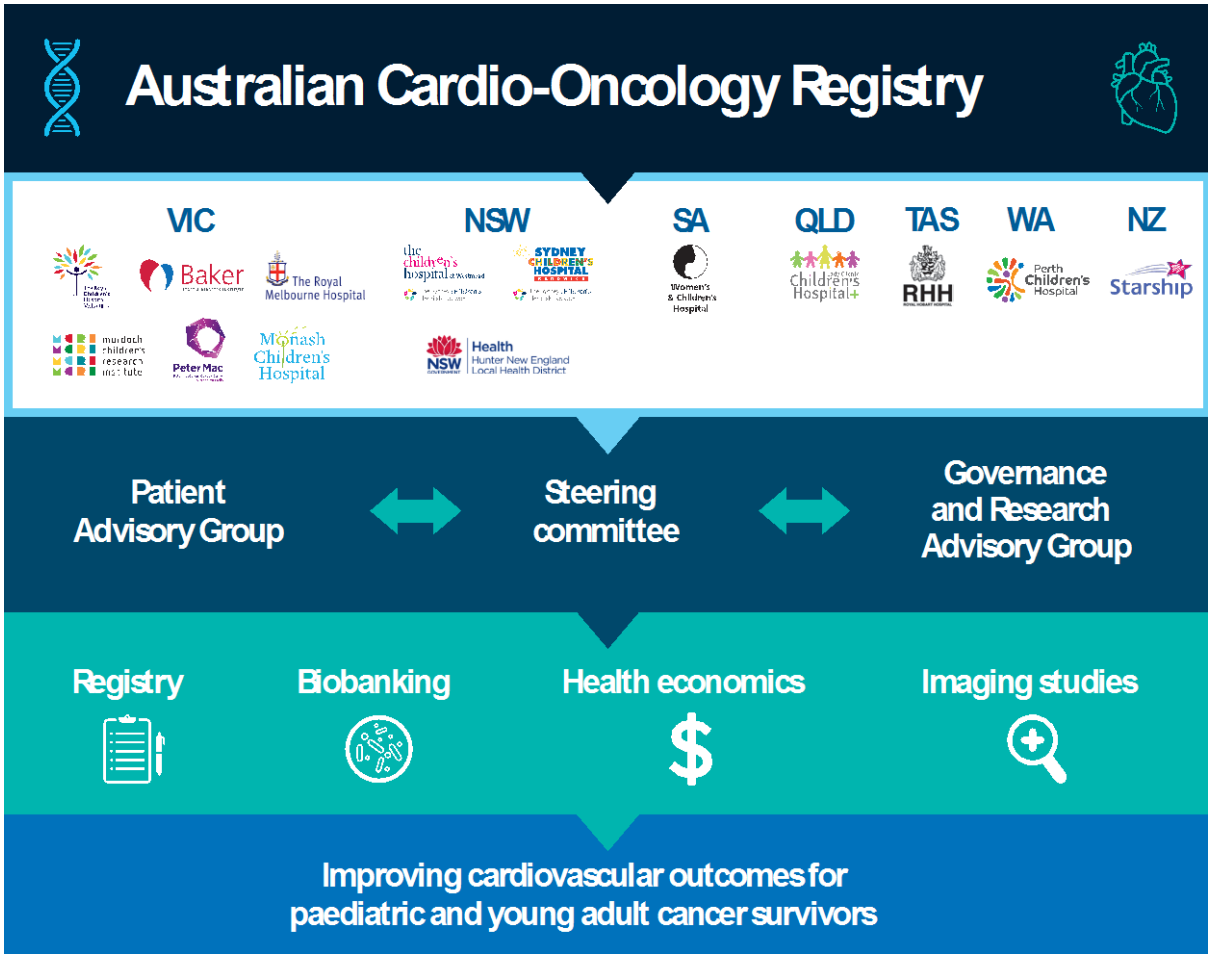

Figure 1: Partners, governance and enrolment arms of the ACOR study. The ACOR study outcomes will include **(a)** Comprehensive clinical phenotyping of all eligible patients exposed to cardiac toxic therapies nationally **(b)** Longitudinal data to monitor cardiac outcomes in paediatric and young adult cancer survivors. **(c)** National Cardio-Oncology Biobank to facilitate further basic science studies. **(d)** State of the art cardiac imaging studies to help guide assessment of cardiac reserve **(e)** Expert steering committee to guide and approve future study developments, analysis and dissemination of results and establish national paediatric cardio-oncology guidelines.

(a) Analysis of Registry Endpoints

Data will be analysed at six-monthly time-points the data will be analysed to determine risk factors, epidemiology, clinical profiles, clinical outcome, management of LVEF, and changes to oncology management as a result of CTRCD. The measured primary outcomes are *(i) Freedom from adverse events* (measured as time related hazards) including death, development of LVEF dysfunction, heart transplantation, arrhythmias, thromboembolic events, hypertension, poor functional status, and initiation of cardiac medication. *(ii) Quality of life and psychological health and well-being* for both children (using the Pediatric Quality of Life Inventory (PedsQL) version 4.0 which includes 4 domains: physical, emotional, social and school functioning) and carer (using the assessment of quality of life 8D (AQoL-8D)). CTRCD will be defined according to the following echocardiographic criteria: a symptomatic decrease in LVEF by more than 5%, an asymptomatic decrease in LVEF by more than 10% to less than 55%, or a reduction in global longitudinal strain (GLS) by 12% or more in any of the echocardiograms conducted at 3, 6, 9, and 12 months post-baseline.

(b) Biobanking

Each participating Institute will biobank their specimens locally. The hosting Institute tissue bank coordinator will organise the transfer of appropriate biological material for specific projects once approved by the Steering Committee. Whole exome and whole genome sequencing will be performed on patients with and without cardiotoxicity as the database matures.

(c) Health Economic analysis to determine (1) the cost and (2) short-term cost-effectiveness of the registry and cardio-oncology clinics, from a government and/or societal perspectives.

Clinical registries have demonstrated utility as a means of improving patient outcomes and the safety and quality of care. Value for money of the creation of ACOR and its clinics in the short-term, within an initial 5-year period, will be assessed by cost-consequences or cost-effectiveness analysis. The cost-effectiveness analysis will compare incremental costs

associated with creation of the ACOR, and clinics, to all incremental outcomes measured in the outcome evaluation (e.g. adverse event mortality case averted or Quality adjusted life year (QALY)) in a cost-consequences analysis. Healthcare in Australia and New Zealand is predominately provided by the Government, thus ACOR will evaluate economic impact from a provider prospective. Costs associated with the implementation of the standardised guidelines and the cardio-oncology clinics will be collected and valued using market value of goods where relevant. Costs associated with health service usage by patients will be collected, linked to individual patient's data from the Medicare Benefit Schedule and Pharmaceutical Benefits Scheme and valued using best available national sources. The goal of this analysis is to provide a platform from which to guide policy decisions made by managers of the healthcare system to ensure maximal positive economic impacts for patients and their families

(d) Extended Cardiac Evaluation

Exercise cardiac magnetic resonance imaging (cMRI) and cardiopulmonary exercise testing are superior for early detection of cardiac dysfunction in adults.(18) Neither of these imaging modalities are routinely used in the paediatric setting. In this context, we saught to utilise ACOR to provide evidence to support the utility of cMRI and exercise testing for early detection of post-therapeutic heart damage in a paediatric and AYA population. To do this a sub-set of patients from two sites will be enrolled in a cardiac functional study (Extended Cardiac Evaluation) building on previous work in an adult population.(18) A pilot study in paediatric and AYA patients has been performed already using cardiopulmonary exercise testing, rest and cMRI. The results show that resting measures of cardiac function are insensitive to significant cardiac dysfunction within the population. This validation study is an exemplar of the range of additional research studies that ACOR will enable in the future.

Discussion

Paediatric and AYA cancer survivors are a patient group with the highest number of life-years saved following a cancer diagnosis. In this context, improving their quality of life and co-morbidities following cancer care is imperative. (19) The establishment of the ACOR is a step towards ensuring improved short and long-term cardiovascular disease outcomes for paediatric

and AYA cancer survivors. As the largest and only population-based cardiotoxicity database of paediatric and AYA oncology patients in the world, and the first paediatric registry that will document cardiotoxicity in response to both chemotherapy and novel targeted therapies using a prospective and longitudinal approach, the study has unique potential to improve our understanding of CTRCD in the modern era. This represents a significant advance over the current localised and ad hoc approach to monitoring CTRCD.

While clinical risk factors for ACT in particular such as younger age at diagnosis and female sex have been identified through previous research, their support has not been universal within the literature.(20-22) This complication is therefore difficult to predict based on such clinical information, suggesting a significant genetic component to its pathophysiology whose further characterisation will assist in developing an effective individualized risk stratification process. ACOR will enable further analysis of genetic profiling for survivors, to assist in risk stratification of the patient cohort. Ultimately, this could lead to 'at-risk' patients being identified at the commencement of their cancer therapy from which risk prevention strategies can be initiated. Risk stratification for CTRCD may allow for individualisation of therapy and thus reduce the incidence of this adverse drug reaction.

Current evaluation of heart function is reliant upon echocardiography. However, this imaging modality on its own has low diagnostic sensitivity and low predictive power in detecting subtle cardiac injury.(16) ACOR will therefore utilise more sophisticated imaging such as exercise CMR and VO2max testing to follow disease progression and establish this modality's role in toxicity monitoring.

Importantly, in terms of health policy development, ACOR will provide a detailed analysis of the health economic impacts of both the registry and a trial of specialised cardio-oncology clinics. This cost-effectiveness profiling is necessary to develop sound policies and guidelines for the management CTRCD.

By identifying the parameters and practices (be that genetic, imaging surveillance, or therapeutics) that lead to long-term survival free of adverse cardiac events, we will develop guidelines that ensure the best quality of life for our patients. This pioneering work provides a

sound platform from which longer-term studies can be initiated, given CTRCD is observed well beyond 20 years post exposure to the drug.

Future perspectives

ACOR is about to publish its first annual review. This review will evaluate the structure, performance, and quality of the data-set to date. Following this, the next outcome (over years 2-3) will be to begin longitudinally documenting the CTRCD phenotype and begin the analysis both the genetic studies that may predispose to this toxicity, and evaluate novel imaging techniques for assessment of cardiac reserve. In an advanced step (approximately years 3-5), ACOR will use the developed cardiotoxicity cellular models to assess the function of genomic variants that predispose to ACT and to discover new cardio-protectant molecules *in vitro*. The culmination of this work will be to create guidelines and policy for paediatric and adolescent patients exposed to cardiotoxicity in the modern era.

Conclusion

As an established partnership of 12 tertiary paediatric and adult tertiary institutes, the ACOR registry and biobank will provide a comprehensive documentation of the current diagnostic and therapeutic approaches to CTRCD across Australia and New Zealand. This registry and biobank will build an evidence base that will inform paediatric and AYA cardio-oncology guidelines, policies and position. In addition, it will provide a research platform from which the mechanisms, pathology, detection and protection against CTRCD can be investigated further.

References

1. Bansal N, Amdani SM, Hutchins KK, Lipshultz SE. Cardiovascular disease in survivors of childhood cancer. Curr Opin Pediatr. 2018;30(5):628-38.

2. Kremer LC, van Dalen EC, Offringa M, Voute PA. Frequency and risk factors of anthracycline-induced clinical heart failure in children: a systematic review. Ann Oncol. 2002;13(4):503-12.

3. Reinbolt RE, Patel R, Pan X, Timmers CD, Pilarski R, Shapiro CL, et al. Risk factors for anthracycline-associated cardiotoxicity. Support Care Cancer. 2016;24(5):2173-80.

4. Blanco JG, Sun CL, Landier W, Chen L, Esparza-Duran D, Leisenring W, et al. Anthracycline-related cardiomyopathy after childhood cancer: role of polymorphisms in carbonyl reductase genes--a report from the Children's Oncology Group. J Clin Oncol. 2012;30(13):1415-21.

5. Semsei AF, Erdelyi DJ, Ungvari I, Csagoly E, Hegyi MZ, Kiszel PS, et al. ABCC1 polymorphisms in anthracycline-induced cardiotoxicity in childhood acute lymphoblastic leukaemia. Cell Biol Int. 2012;36(1):79-86.

6. Falduto A, Cimino F, Speciale A, Musolino C, Gangemi S, Saija A, et al. How gene polymorphisms can influence clinical response and toxicity following R-CHOP therapy in patients with diffuse large B cell lymphoma. Blood Rev. 2017;31(4):235-49.

7. Wojnowski L, Kulle B, Schirmer M, Schluter G, Schmidt A, Rosenberger A, et al. NAD(P)H oxidase and multidrug resistance protein genetic polymorphisms are associated with doxorubicin-induced cardiotoxicity. Circulation. 2005;112(24):3754-62.

8. Rossi D, Rasi S, Franceschetti S, Capello D, Castelli A, De Paoli L, et al. Analysis of the host pharmacogenetic background for prediction of outcome and toxicity in diffuse large B-cell lymphoma treated with R-CHOP21. Leukemia. 2009;23(6):1118-26.

9. Lancellotti P, Anker SD, Donal E, Edvardsen T, Popescu BA, Farmakis D, et al. EACVI/HFA Cardiac Oncology Toxicity Registry in breast cancer patients: rationale, study design, and methodology (EACVI/HFA COT Registry)--EURObservational Research Program of the European Society of Cardiology. Eur Heart J Cardiovasc Imaging. 2015;16(5):466-70.

10. Genuino AJ, Chaikledkaew U, The DO, Reungwetwattana T, Thakkinstian A. Adjuvant trastuzumab regimen for HER2-positive early-stage breast cancer: a systematic review and meta-analysis. Expert Rev Clin Pharmacol. 2019;12(8):815-24.

11. Totzeck M, Mincu RI, Rassaf T. Cardiovascular Adverse Events in Patients With Cancer Treated With Bevacizumab: A Meta-Analysis of More Than 20 000 Patients. J Am Heart Assoc. 2017;6(8).

12. Chu TF, Rupnick MA, Kerkela R, Dallabrida SM, Zurakowski D, Nguyen L, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. Lancet. 2007;370(9604):2011-9.

13. Wada T, Ando K, Naito AT, Nakamura Y, Goto A, Chiba K, et al. Sunitinib does not acutely alter left ventricular systolic function, but induces diastolic dysfunction. Cancer Chemother Pharmacol. 2018;82(1):65-75.

14. Francisco ARG, Alves D, David C, Guerra L, Pinto FJ, Almeida AG. Cardiotoxicity in Hematological Diseases: Are the Tyrosine Kinase Inhibitors Imatinib and Nilotinib Safe? Cardiovasc Toxicol. 2018;18(5):431-5.

15. Loar RW, Noel CV, Tunuguntla H, Colquitt JL, Pignatelli RH. State of the art review: Chemotherapy-induced cardiotoxicity in children. Congenit Heart Dis. 2018;13(1):5-15.

16. Conyers R, Costello B, La Gerche A, Tripaydonis A, Burns C, Ludlow L, et al. Chemotherapy-related cardiotoxicity: are Australian practitioners missing the point? Intern Med J. 2017;47(10):1166-72.

17. Snipelisky D, Park JY, Lerman A, Mulvagh S, Lin G, Pereira N, et al. How to Develop a Cardio-Oncology Clinic. Heart Fail Clin. 2017;13(2):347-59.

18. Beaudry RI, Howden EJ, Foulkes S, Bigaran A, Claus P, Haykowsky MJ, et al. Determinants of exercise intolerance in breast cancer patients prior to anthracycline chemotherapy. Physiol Rep. 2019;7(1):e13971.

19. Ryan D CR, Hodgkinson K, Chan K, Stringer K, Moorehead P. Interventions to improve the aftercare of survivors of childhood cancer: A systematic review. Pediatric Hematology Oncology Journal. 2018;3(4):90-8.

20. Moussa E, Zamzam M, Kamel A, Salah Z, Attia I, Gaber L, et al. Risk stratification and pattern of cardiotoxicity in pediatric Ewing sarcoma. J Egypt Natl Canc Inst. 2017;29(1):53-6.

21. Rathe M, Carlsen NL, Oxhoj H, Nielsen G. Long-term cardiac follow-up of children treated with anthracycline doses of 300 mg/m2 or less for acute lymphoblastic leukemia. Pediatr Blood Cancer. 2010;54(3):444-8.

22. Paulides M, Kremers A, Stohr W, Bielack S, Jurgens H, Treuner J, et al. Prospective longitudinal evaluation of doxorubicin-induced cardiomyopathy in sarcoma patients: a report of the late effects surveillance system (LESS). Pediatr Blood Cancer. 2006;46(4):489-95.

The Australia and New Zealand Cardio-Oncology Registry (ACOR): evaluation of chemotherapy-related cardiotoxicity in a national cohort of paediatric cancer patients

1. Daniel Lapirow Medicine, Dentistry and Health Sciences, The University of Melbourne, Grattan Street, Parkville, VIC 3010, Australia. *Contribution* – primary author of manuscript.
2. Andre La Gerche Head Cardiac Imaging Research. Baker Heart and Diabetes Institute, 75 Commercial Road, Melbourne, Victoria 3004, Australia *Contribution* – primary investigator on imaging studies for ACOR. Steering committee member. Editing of manuscript.
3. Claudia Toro Children's Cancer Centre, The Royal Children's Hospital, 50 Flemington Road, Parkville, VIC 3052, Australia. *Contribution* – Masters Student with University of Melbourne leading imaging studies at Baker IDI. Editing of manuscript.
4. Emma Masango Murdoch Children's Research Institute, The Royal Children's Hospital, 50 Flemington Road, Parkville, VIC 3052, Australia. *Contribution*- National Co-ordinator Australian Cardio-Oncology Registry. Ethics applications nationally and coordination of on-boarding of the study. Editing of Manuscript.
5. Ben Costello Baker Heart and Diabetes Institute, 75 Commercial Road, Melbourne, Victoria 3004, Australia. *Contribution*- Co-primary investigator on imaging studies for ACOR. Steering committee member. Editing of manuscript.
6. Enzo Porrello - Murdoch Children's Research Institute, The Royal Children's Hospital, 50 Flemington Road, Parkville, VIC 3052, Australia. Department of Physiology, The University of Melbourne, Grattan Street, Parkville, VIC 3010, Australia. *Contribution* - Lead of Cardiac Regeneration MCRI. Steering Committee Member. Editing of Manuscript.
7. Louise Ludlow Murdoch Children's Research Institute, The Royal Children's Hospital, 50 Flemington Road, Parkville, VIC 3052, Australia and the Children's Cancer Centre, The Royal Children's Hospital, 50 Flemington Road, Parkville, VIC 3052, Australia. *Contribution*- Tissue Bank Co-ordinator providing oversight of national biobank. Editing of manuscript.

8. Glenn Marshall University of New South Wales, High St, Kensington, NSW 2052, Australia. Head of Children's Oncology Department Randwick Children's Hospital. *Contribution* - Steering Committee Member. Editing of Manuscript
9. Toby Trahair - Sydney Children's Hospital Randwick, High St, Randwick, NSW 2031, Australia. *Contribution* - Steering Committee Member. Editing of Manuscript
10. Marion Mateos - Sydney Children's Hospital Randwick, High St, Randwick, NSW 2031, Australia.Steering Committee Member. Editing of Manuscript
11. Jeremy Lewin Peter MacCallum Cancer Centre, 305 Grattan Street, Melbourne, VIC 3004, Australia. *Contribution* – Primary site investigator. Steering Committee Member. Editing of Manuscript.
12. Jennifer Byrne The Children's Hospital at Westmead, Corner Hawkesbury Road and Hainsworth Street, Westmead 2145, Australia . Discipline of Child and Adolescent Health, The University of Sydney, The Children's Hospital at Westmead, Corner Hawkesbury Road and Hainsworth Street, Westmead 2145, Australia. *Contribution*- Co-ordination of national biobanking program. Steering Committee Member. Editing of manuscript.
13. Rose Boutros - The Children's Hospital at Westmead, Corner Hawkesbury Road and Hainsworth Street, Westmead 2145, Australia. *Contribution* – Steering Committee Member. Editing of manuscript.
14. Rebecca Manudhane - The Michael Rice Centre, Women's and Children's Hospital, 72 King William Road, North Adelaide, SA 5006, Australia. *Contribution* – Steering Committee Member. PI Adelaide. Editing of Manuscript.
15. John Heath - Paediatric Oncology, Royal Hobart Hospital, 48 Liverpool Street, Hobart, TAS 7000, Australia. *Contribution* – Steering Committee Member. PI Tasmania. Editing of Manuscript.
16. Julian Ayer, The Children's Hospital at Westmead, Corner Hawkesbury Road and Hainsworth Street, Westmead 2145, Australia. *Contribution* – Steering Committee Member. PI New South Wales. Editing of Manuscript.
17. Melissa Gabriel - The Children's Hospital at Westmead, Corner Hawkesbury Road and Hainsworth Street, Westmead 2145, Australia. *Contribution* – Steering Committee Member. PI New South Wales. Editing of Manuscript.
18. Thomas Walwyn - Perth Children's Hospital, 15 Hospital Avenue, Nedlands, WA 6009, Australia. *Contribution* – Steering Committee Member. PI Perth. Editing of Manuscript.

19. Jelena Saundankar Perth Children's Hospital, 15 Hospital Avenue, Nedlands, WA 6009, Australia. *Contribution* – Steering Committee Member. PI Perth. Editing of Manuscript.
20. Jonathon Forsey - Sydney Children's Hospital Randwick, High St, Randwick, NSW 2031, Australia. *Contribution* – Steering Committee Member. PI Sydney. Editing of Manuscript.
21. Ha Le - School of Health and Soc. Dev, Deakin University, 221 Burwood Highway Burwood VIC 3125, Australia. Murdoch Children's Research Institute, The Royal Children's Hospital, 50 Flemington Road, Parkville, VIC 3052, Australia. *Contribution*- Lead of Health Economic Analysis. Editing of Manuscript.
22. Kylie Mason - Clinical Haematology and Bone Marrow Transplant Service, The Royal Melbourne Hospital, 300 Grattan Street (corner of Royal Parade), Parkville, VIC 3050, Australia. *Contribution* – PI RMH. Steering Committee Member. Editing of Manuscript.
23. David Celermajer - Cardiology Department, The Royal Prince Alfred Hospital, Level 11,KGV Building Missenden Road, Camperdown, NSW 2050, Australia. *Contributions* – Steering Committee Member. Editing of Manuscript.
24. Peter Downie - Children's Cancer Centre, Monash Health, Monash Children's Hospital, 246 Clayton Road, Clayton , VIC 3168, Australia *Contributions* - Steering Committee Member. Editing of Manuscript.
25. Roderick Walker - Queensland Children's Hospital, 501 Stanley St, South Brisbane, QLD 410, Australia. *Contributions* - Steering Committee Member. Editing of Manuscript.
26. Lucy Holland - Queensland Children's Hospital, 501 Stanley St, South Brisbane, QLD 410, Australia. *Contributions* - Steering Committee Member. Editing of Manuscript.
27. Michelle Martin - Children's Cancer Centre, The Royal Children's Hospital, 50 Flemington Road, Parkville, VIC 3052, Australia. *Contributions* – Patient recruitment, processing of biobank samples, Editing of Manuscript.
28. Lorna McLeman - Children's Cancer Centre, The Royal Children's Hospital, 50 Flemington Road, Parkville, VIC 3052, Australia. *Contributions* – Patient recruitment, processing of biobank samples, Editing of Manuscript.

29. Yonatan Diamond - Children's Cancer Centre, The Royal Children's Hospital, 50 Flemington Road, Parkville, VIC 3052, Australia. *Contributions* – Patient recruitment, processing of biobank samples, Editing of Manuscript.
30. Maurizio Marcocci - My Room Children's Cancer Charity, 64-90 Sutton St, North Melbourne, VIC 3051, Australia. *Contribution* - Lead of patient advocacy group. Editing of Manuscript.
31. Michael Cheung - Department of Cardiology, The Royal Children's Hospital, 50 Flemington Road, Parkville, VIC 3052, Australia. *Contribution* – Steering Committee Member. Editing of Manuscript.
32. David A. Elliott*[1,4] Murdoch Children's Research Institute, The Royal Children's Hospital, 50 Flemington Road, Parkville, VIC 3052, Australia. Department of Paediatrics, The University of Melbourne, Grattan Street, Parkville, VIC 3010, Australia *Contribution* – Lead of scientific studies in ACOR. Co-lead on ACOR establishment. Chair of Steering Committee. Editing of Manuscript.
33. Rachel Conyers *[1] Murdoch Children's Research Institute, The Royal Children's Hospital, 50 Flemington Road, Parkville, VIC 3052, Australia. Children's Cancer Centre, The Royal Children's Hospital, 50 Flemington Road, Parkville, VIC 3052, Australia. Medicine, Dentistry and Health Sciences, The University of Melbourne, Grattan Street, Parkville, VIC 3010, Australia. *Contributions* - Lead of clinical studies in ACOR. Co-lead on ACOR establishment. Chair of Steering Committee. Editing of Manuscript.

*contributed equally

Corresponding Author

Associate Professor Rachel Conyers
Children's Cancer Centre
The Royal Children's Hospital
50 Flemington Road, Parkville, VIC 3052, Australia.
Email Rachel.conyers@rch.org.au
Phone 03 9345 5656

Acknowledgements

The ACOR steering committee and principal investigators would like to acknowledge; the patients and families that contributed to this research. Professor Melissa Little the Theme Director of Cell Biology and the Cardiac Regeneration laboratory at the Murdoch Children's

Research Institute and the Clinician Scientist Fellowship Scheme at the Murdoch Children's Research Institute. Study data was collected and managed using REDCap electronic data capture tools hosted at Murdoch Children's Research Institute. The ACOR is funded through grants from The Royal Children's Hospital Foundation, The Royal Australasian College of Physicians and Kids Cancer Project. The authors have no industrial links or affiliations.

Keywords Cardio-oncology, biobank, registry, paediatric cancer, Australian registries, Australian Cardio-oncology registry, ACOR, genetics, anthracycline, cardiotoxicity