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BMJ Open Protocol: Can coronary artery calcium score identified on thoracic planning CT scans be used and actioned to identify cancer survivors at high risk of cardiac events: A feasibility study in cancer survivors undergoing radiotherapy in Australia

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ABSTRACT

Introduction A coronary artery calcium (CAC) CT scan can identify calcified plaque and predict risk of future cardiac events. Cancer survivors undergoing thoracic radiotherapy routinely undergo a planning CT scan, which presents a unique opportunity to use already obtained medical imaging to identify those at the highest risk of cardiac events. While radiation therapy is an important modality for many cancer treatments, radiation dose to the heart in thoracic radiotherapy leads to cardiotoxicity and may accelerate pre-existing atherosclerosis. The primary aims of this study are to investigate the feasibility of using CAC scores calculated on thoracic radiotherapy planning CT scans to identify a subset of cancer survivors at an increased risk of future cardiac events, and to establish and evaluate a referral pathway for assessment and management in a cardio-oncology clinic. An optional substudy aims to investigate using abdominal aortic calcification (AAC) as a practical, low-radiation alternative to CAC to evaluate and monitor vascular health.

Methods and analysis This is an observational, prospective study in a minimum of 100 cancer survivors commencing radiotherapy. Participants will have CAC scored from thoracic radiotherapy planning CT scans. Those identified as high risk (CAC score>0) will be referred to a cardio-oncology clinic. Feasibility, determined by adherence to the recommended pathway, and impact on quality of life and anxiety measured via questionnaire, will be assessed. Participants in Western Australia will be invited to participate in a 12-month observational pilot substudy, investigating lifestyle behaviours and the use of a dual-energy X-ray absorptiometry machine to measure musculoskeletal health and AAC.

Ethics and dissemination Ethics approval has been obtained from St Vincent's Hospital, Sydney (Project number 2021/ETH11847), GenesisCare and Edith Cowan University (2022-03326-DALLAVIA). Study results will be reported in peer-reviewed academic journals, at scientific

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study will provide nationally representative evidence for the use of coronary artery calcium (CAC) scoring and a cardiology referral pathway in routine clinical practice for cancer survivors and clinicians.
- ⇒ The study will be completed within private oncology and cardiology clinics within Australia, so findings may not be generalisable to the public healthcare system.
- ⇒ CAC scoring requires a chest CT scan, so the study sample will only include those receiving thoracic radiotherapy (predominantly breast and lung cancer) and findings will not be generalisable to other cancer populations.

conferences, and at clinical forums, irrespective of the results observed.

Trial registration number ACTRN12621001343897.

INTRODUCTION

As cancer treatments and survival outcomes are improving, there is a greater focus on survivorship and management of late toxicity from treatment. Despite improving prevention and treatment of both cardiovascular disease (CVD) and cancer, they remain the two leading causes of death in the developed world.¹ Furthermore, among cancer survivors alive 5 years after diagnosis, CVD-related deaths are shown to exceed cancer-related deaths from 13 years after cancer diagnosis.² Radiation is an important modality for many cancer treatments in both the definitive and adjuvant settings. However, radiation dose to



the heart in thoracic radiotherapy may lead to cardiac toxicity or accelerate underlying atherosclerosis.^{3,4} Accelerated atherosclerosis is an important mechanism in the development of radiation induced cardiac disease and has the potential to lead to morbidity and mortality, and impose significant burden on the health system.^{5,6} The risk of acute coronary events is shown to increase by 7.4%–16.5% per Gray of mean heart radiation dose.^{4,7} Although modern delivery of radiotherapy involves substantially lower doses to the heart compared with older techniques, in many cases, the heart still receives a significant dose (~2.4 Gray).^{8,9}

Coronary artery disease is due to atheromatous plaques forming in the arteries that supply the musculature of the heart. A coronary artery calcium (CAC) CT scan is able to identify calcified plaque burden and is widely used to predict risk of future cardiac events in otherwise asymptomatic individuals.^{10,11} Calcium scoring provides an improvement in risk stratification beyond that of traditional risk factors in asymptomatic individuals.^{12,13} Indeed, individuals with no traditional risk factors for coronary heart disease but an elevated CAC score have been shown to have a 3.5 times higher risk of a coronary heart disease event compared with individuals with ≥ 3 risk factors and a CAC score of 0.¹⁰ The gold-standard approach has been to use dedicated, ECG-triggered scans to calculate CAC and risk stratify based on results. However, it has been shown that untriggered CAC CT scans performed for other purposes can accurately identify individuals at high risk of developing acute coronary events.¹⁴

Cancer survivors undergoing thoracic radiotherapy routinely undergo a CT scan for simulation and planning purposes, presenting a unique opportunity to use already obtained medical imaging to identify those with pre-existing CAC who are at highest risk of future cardiac events. In breast cancer survivors treated with adjuvant radiotherapy, high pretreatment CAC score, calculated on planning CT scans, was shown to be independently associated with increased incidence of acute coronary events.¹⁵ Furthermore, CAC score, but not the traditional Framingham Risk Score, was shown to predict the incidence of composite clinical events (all-cause mortality and cardiac events combined) as well as cardiac events in breast cancer survivors.¹⁶ Strategies to prevent cardiac events may also be important from a cancer perspective, with early-stage breast cancer survivors who experience a postdiagnosis cardiac event shown to have an increased risk of cancer recurrence and breast cancer-specific mortality.¹⁷ Overall, it appears that CAC scoring can identify cancer survivors with underlying atherosclerosis that would benefit from primary and secondary preventative measures.¹⁵ However, no known study has investigated actioning CAC scoring by referring high-risk cancer survivors to a cardio-oncology clinic.

The abdominal aorta is another site where arterial calcification can be measured, often preceding the development of CAC.¹⁸ Abdominal aortic calcification (AAC) is related to CAC and also strongly predicts CVD

hospitalisations and deaths in the general population.¹⁸ Notably, AAC has been shown to predict incident CVD in the absence of CAC.¹⁹ Furthermore, AAC has been shown to independently predict incident CVD independent of CAC.²⁰ AAC can be easily assessed using a dual-energy X-ray absorptiometry (DXA) machine with substantially lower levels of radiation compared with CAC imaging.^{21,22} Therefore, AAC may be a safe and practical method for serial monitoring of arterial calcification and CVD risk; however, no known studies have assessed AAC in cancer survivors. Understanding the relationship between DXA-assessed AAC and CT-assessed CAC in cancer survivors may also have important implications for cancer survivors who do not undergo routine CT scans, where measurement of AAC using DXA may be a way to screen for elevated CVD risk with negligible radiation. Importantly, DXA can also be used to measure bone density and body composition, which is valuable given evident musculoskeletal adverse effects of certain cancer treatments.²³

Consistent evidence suggests that cancer survivors benefit from maintaining a healthy diet and regular physical activity throughout the care continuum, including ameliorating cancer treatment-related cardiovascular and musculoskeletal adverse effects.²⁴ Poor diet and insufficient physical activity are shared risk factors for CVD and many cancers,²⁵ and have been shown to negatively impact cancer recurrence and overall survival after diagnosis.^{24,26,27} Despite this, many cancer survivors do not engage in sufficient physical activity and have suboptimal diets, including not meeting guidelines for fruit and vegetable intake.²⁸ Cancer treatment combined with the detection of raised arterial calcification or impaired musculoskeletal health may present a teachable moment to promote healthful lifestyle behaviour change, including dietary modification and increased physical activity.

This will be the first known study to investigate the feasibility of using thoracic radiotherapy planning CT scans to calculate CAC score, and subsequently refer those considered to be at high cardiovascular risk to cardiology for assessment and management. The optional substudy will be the first to investigate the use of images from DXA machines for monitoring cardiovascular risk in a cancer population.

Objectives

The primary aims of this study are to investigate the feasibility of using CAC scores calculated on thoracic radiotherapy planning CT scans to identify a subset of cancer survivors that are at highest background risk of future cardiac events based on their baseline CAC score, and to establish and evaluate a referral pathway for assessment and management in a cardio-oncology clinic. Secondary objectives are as follows: (1) to investigate the impact of providing CAC scores on participant's quality of life (QoL) and anxiety and (2) to investigate adherence to the cardio-oncology pathway (for those referred).

The primary objective of the optional substudy is to assess AAC in cancer survivors prior to radiotherapy

and at 12 months follow-up. Secondary objectives of the substudy are as follows: (1) to assess the relationship between DXA-assessed AAC and CT-assessed CAC; (2) to assess bone mineral density (BMD) and body composition in cancer survivors prior to radiotherapy and at 12 months follow-up; (3) to assess lifestyle factors such as diet, physical activity and sedentary behaviour in cancer survivors prior to radiotherapy and at 12 months follow-up and (4) to understand cancer survivor's experiences of receiving lifestyle advice during treatment.

METHODS

Study design

This will be an observational, prospective study. The study complies with the Standard Protocol Items: Recommendations for Interventional Trials guidelines for the minimum content of a clinical trial protocol.²⁹ Cancer survivors commencing radiotherapy will have CAC scored from their thoracic radiotherapy planning CT scan. Those identified as high risk (CAC score > 0) will be referred to a cardio-oncology clinic. High-risk cancer survivors will be defined as those with a CAC score > 0, given published data suggesting untriggered CT CAC scores may underestimate high CAC scores.¹⁴ Feasibility, as defined by adherence to the recommended pathway, and impact on QoL and anxiety will be observed.

Optional substudy

Participants enrolled in the primary study who reside in Western Australia will be invited to also participate in an optional 12-month observational substudy, irrespective of their CAC score. In addition to the measures observed in the primary study, participants in the substudy will complete a set of DXA images (hip, spine, whole-body and lateral spine) and a series of validated lifestyle questionnaires at baseline and after 12 months. DXA image results, including measures of vascular and musculoskeletal health, will be provided to the treating clinician. Substudy participants will be invited to complete semi-structured interviews at the completion of radiotherapy about their experiences receiving diet and physical activity advice during treatment.

Patient and public involvement

Cancer survivor representatives reviewed and provided feedback on the participant information and consent form used in the study, which described the study design and the outcomes assessed. However, neither patients nor members of the public were involved in the study design or objectives.

Participants

Eligible participants will be aged 18 years or older with histologically or cytologically confirmed malignancy who are undergoing thoracic CT for radiotherapy planning and receiving radiotherapy with curative intent as part of standard treatment for malignancy. Participants in the

optional substudy will reside in Western Australia. Participants will be excluded if they are pregnant or lactating, have known coronary artery disease, are currently under the care of a cardiologist, have a life expectancy less than 5 years, or for any other reason which, in the opinion of the study investigators, would adversely impact the participant's ability to participate in the study safely and fully (eg, poor health literacy, mental health disorder, vulnerable participant with poor social support).

Recruitment and screening

Potential participants will be identified by prescreening cancer survivors planned for radiation therapy with curative intent who undergo a thoracic planning CT scan at participating GenesisCare sites in Western Australia, South Australia, Queensland, Victoria and New South Wales. Recruitment will begin in July 2022 and will end in July 2023 or continue until the minimum target sample of 100 participants is reached. A member of the site's study team will prescreen health records for potentially eligible cancer survivors. All potential study participants will be contacted by site personnel following initial consultation with their treating clinician to invite them to consider participation. Those interested will be shown a video outlining all aspects of the study in lay language and a provided a copy of the participant information sheet and consent form (PICF) to view, read and discuss with family, general practitioners, specialists, etc. The site personnel will discuss the study again with the potential participant once they have had time to consider the study and will answer all questions the participant has. Where required, they will be referred back to the treating clinician to answer any clinical questions not otherwise able to be answered by the personnel conducting the informed consent process. Eligible cancer survivors who are willing to proceed will be asked to provide written informed consent prior to initiating any study procedures.

Participants enrolled in the primary study in Western Australia will be invited to participate in the optional substudy. They will be provided with the substudy PICF at the same time as the primary study PICF. If the participant is interested in taking part in the substudy, their contact details will be provided to the substudy research staff who will contact the participant to explain the substudy and answer any questions they have. Substudy-specific written informed consent will then be collected as per the above processes.

Assessments

The study flow chart is presented in [figure 1](#). Study assessments will be completed via face-to-face clinic visits where these align with the participant's standard of care treatment appointments, or remotely via telehealth. Participants will undergo their radiotherapy planning CT as per standard of care procedures (ie, not a study-specific procedure). Baseline assessments will be completed before or after this radiotherapy planning CT scan. If completed after, assessments will be completed within the first week

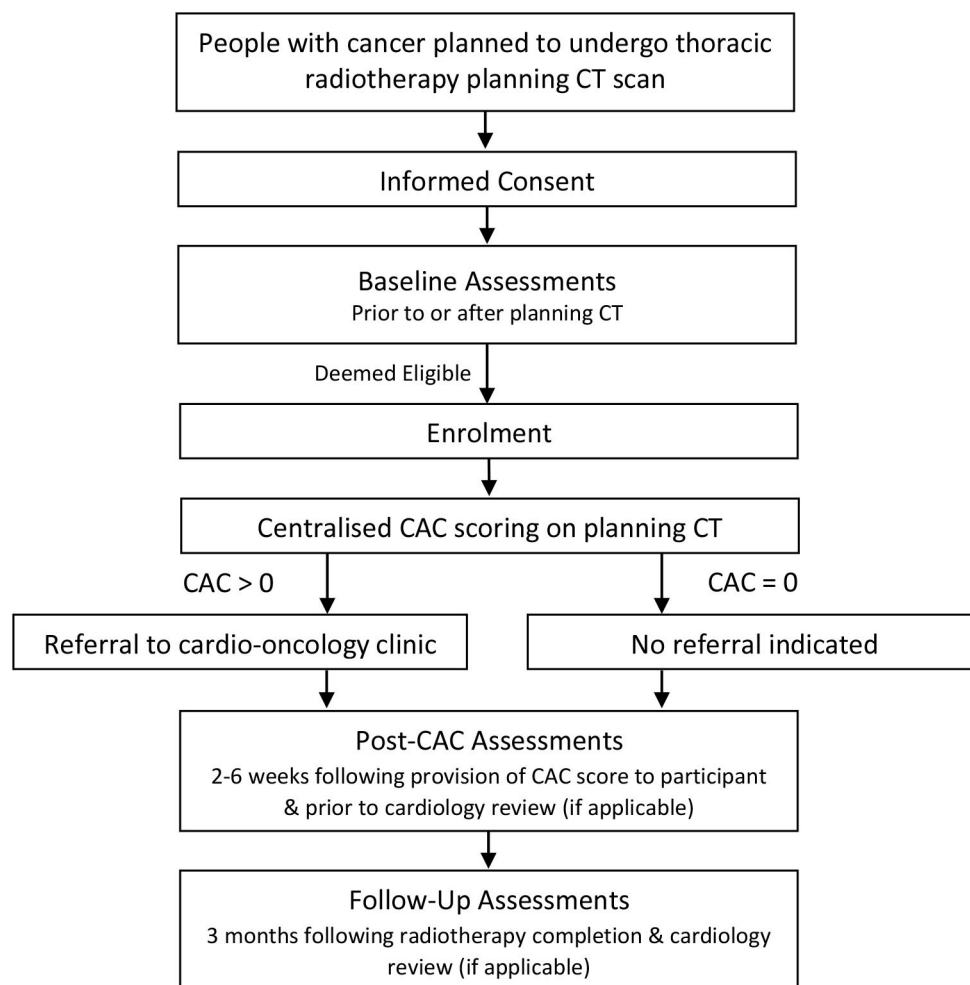


Figure 1 Study flow chart. CAC, coronary artery calcium.

of radiotherapy treatment. The baseline visit will include collection of demographic information, cardiac risk factors, cardiac and cancer history, COVID-19 history and vaccination, current medications, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, planned radiotherapy information, and assessment of QoL and anxiety. Once baseline assessments have been completed, CAC will be measured from the radiotherapy planning CT. The CAC score will be reported back to the study site and discussed with the participant, who will be referred to cardiology if indicated. QoL and anxiety will be assessed 2–6 weeks following provision of CAC score to participants, and prior to cardiology review for those referred. Follow-up assessment of QoL and anxiety will be completed for all participants 3 months after completing radiotherapy. For those referred to cardiology, adherence to cardiology referral pathway as well as cardiology investigations as clinically appropriate will also be assessed 3 months after completing radiotherapy. The schedule of assessments is outlined in [table 1](#).

Optional substudy

The study flow chart for the optional substudy is presented in online supplemental figure 1. Participants in the optional substudy will complete an additional set of

assessments. Baseline assessments will be completed prior to or within 4 weeks of commencing radiotherapy. This will include a face-to-face appointment at the imaging facility where they will complete a series of DXA scans, as well as online questionnaires assessing diet, physical activity, sedentary behaviour and readiness to change lifestyle. Within 6 weeks of completing radiotherapy, participants will be invited to participate in a semistructured interview via videoconference. Twelve months following baseline assessments, participants will attend another appointment at the imaging facility to repeat the same set of DXA scans and complete the same set of online lifestyle questionnaires. The schedule of assessments for the optional substudy is outlined in online supplemental table 1.

Outcome measures

Primary study

Primary outcome measure

CAC scoring

The radiotherapy planning CT will initially be analysed automatically by software to differentiate CAC scores of zero and non-zero. This is existing standard software and is not specific to the research study. Non-zero scans will be forwarded for review by a central cardiologist to

Table 1 Schedule of assessments

Assessment	Baseline Pre-CAC scoring	CAC scoring	Post-CAC Scoring 2–6 weeks postscore and precardiology review if applicable	Follow-up or discontinuation 3 months postradiotherapy and cardiology review if applicable
Informed consent	X			
Eligibility assessment	X			
Demographics	X			
Cardiac risk factors	X			
Cardiac history	X			
Cancer history	X			
Current medications	X			
COVID-19 history and vaccination	X			
Vital signs	X			
ECOG performance status	X			
Radiotherapy planning CT scan	X			
Planned radiotherapy information	X			
GAD-7 questionnaire	X		X	X
EQ-5D-5L questionnaire	X		X	X
CAC scoring		X		
Referral to cardiology if clinically indicated		X		
Adherence to recommended pathway (if applicable)				X
Cardiology investigations if applicable				X

CAC, coronary artery calcium; ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, 5-level EQ-5D; GAD-7, Generalised Anxiety Disorder 7.

provide an absolute measurement of CAC. The CAC score will be reported back to the study site. The treating clinician will discuss the result with the participant and if clinically indicated (ie, CAC>0) refer the participant to cardiology.

Secondary outcome measures

Participant characteristics

Data collected at baseline from electronic medical records will include demographics (ie, age and sex), cardiac risk factors (ie, smoking, alcohol use, family history), cardiac history (ie, prior cardiac events, diabetes, hypertension, dyslipidaemia, other vascular disease), cancer history (ie, type, date of diagnosis, stage and prior therapies for any previous cancers), COVID-19 history and vaccination, and current medications. Vital signs including temperature, pulse rate, respiratory rate, blood pressure, height and weight will be collected from standard of care nursing assessments documented in the participant's medical record (height and weight will be measured if not in medical record). Level of functioning will be assessed using the ECOG Performance Status Scale.³⁰ Planned radiotherapy information (ie, location, technique, dosing), as well as information regarding any concomitant or previous therapies for the current cancer, will be collected.

QOL and anxiety

Health-related QoL and anxiety will be assessed using online questionnaires completed at baseline, 2–6 weeks after a participant receives their CAC score, and 3 months following radiotherapy completion. QoL will be assessed using the 5-level EQ-5D questionnaire (EQ-5D-5L).³¹ Anxiety will be assessed using the General Anxiety Disorder 7 questionnaire.³²

Adherence to cardiology referral pathway

For participants referred to cardiology, adherence to the cardiology referral pathway will be assessed by tracking attendance to scheduled cardiology appointments.

Cardiology investigations

Cardiology investigations for those referred will be completed as required per standard of care, which may include ECG, echocardiogram and blood testing (complete blood picture, biochemistry including creatinine clearance, liver function tests, creatine kinase and a fasting lipid profile). Data from these cardiology investigations will be collected from the participant's medical record.

Optional substudy

Primary outcome measure

Abdominal aortic calcification

AAC will be assessed from a lateral spine image from the DXA machine. DXA scans will be performed at Gairdner Bone Densitometry Services, Sir Charles Gairdner Hospital, using the latest fan beam technology (Hologic Horizon A densitometer). AAC will be scored by experts in densitometric imaging using a semiquantitative scoring system (scored 0–24; AAC24), as described in detail previously.^{33–35} DXA scan results, including AAC score, bone density and body composition, will be provided to the treating clinician of each participant.

Secondary outcome measures

BMD and body composition

BMD and body composition will be assessed using DXA as described above. BMD will be assessed using DXA scans of the proximal femur (total hip, femoral neck) and lumbar spine. Total and regional (arms and legs) lean mass and fat mass will be assessed from a total body DXA scan.

Questionnaires

A link for a series of questionnaires to be completed online will be sent to participants at baseline and 12 months, as described below. Dietary intake will be assessed using the Dietary Questionnaire for Epidemiological Studies (DQES), which is a semiquantitative food frequency questionnaire developed by the Cancer Council of Victoria.³⁶ Physical activity will be assessed using the Community Healthy Activities Model Programme for Seniors questionnaire.³⁷ Sedentary time will be assessed using the Longitudinal Aging Study Amsterdam Sedentary Behaviour Questionnaire.³⁸ Readiness to change lifestyle will be assessed using the Readiness to Change and Well-being Questionnaire Readiness to Change and Well-being, which is a behaviour modification questionnaire (developed by the WorkStrong programme, University of California system wide programme) that focuses on individuals' readiness to change over seven different aspects (life satisfaction, energy, weight, exercise, nutrition, health and stress, and mental health).

Semistructured interviews

Perceptions of diet and physical activity support will be assessed using semistructured interviews completed over telephone or via videoconferencing. Participants will be asked questions to explore themes related to key topic areas of supportive care, in particular diet and exercise support, received during cancer treatment. The interviews will be semistructured, so will follow the themes across the topic areas that arise during each discussion rather than following a strict set of specific questions.

Data management

All participant data relating to the study will be recorded in electronic case report forms within the Castor electronic data capture system (Castor, Amsterdam, Netherlands). The Castor system will be used to deliver questionnaires

electronically and to capture the results. The only exception is the DQES included in the optional substudy. For the DQES, participants will be emailed a link via the Castor system to the questionnaire that is delivered and analysed by Cancer Council Victoria. Participants will have the option to complete paper versions of the questionnaires if necessary. The online questionnaires have been designed with mandatory answers required to avoid missing data. Data from clinic assessments and any paper questionnaires will be checked for completeness and entered into the electronic database by a study investigator. Essential study documents and source documentation will be retained for 15 years after completion of the study. Documents will be securely stored, and access restricted to authorised personnel.

Sample size

This is a feasibility study, therefore, the sample size was not calculated based on statistical modelling. A sample size of 100 participants will allow the true proportion with CAC>0 to be estimated to within 0.10 with 95% CI and is large enough to determine whether CAC score calculation is feasible and determine adherence to recommended pathways and impact on QoL for the main study. Accrual within the recruitment period will not be capped, therefore, the minimum target of 100 participants may be exceeded. Recruitment to the optional substudy will be dependent on the main study and will include as many participants as possible that are eligible.

Statistical analysis

Statistical analysis will be performed using SPSS (V.27, IBM) and/or Stata (V.15, StataCorp). Data will be assessed for outliers and normality prior to analysis and transformed if necessary. A significance level of $p < 0.05$ will be adopted for all statistical tests.

Descriptive statistics will be used to report participant characteristics at baseline, adherence to the cardio-oncology pathway for those referred, and clinician survey responses evaluating feasibility of the pathway. CAC score will be reported as a continuous variable, while prevalence and severity of CAC will be reported categorically. Where possible, the sample will be stratified to compare CAC across basic demographic factors and other relevant factors. Repeated measures analyses will be used to identify any changes in QoL and anxiety over the course of the study.

Optional substudy

AAC presence (present or absent) and extent (low, moderate, extensive or high) will be reported categorically. Correlation analysis will be used to assess the relationship between CAC and AAC-24 scores at baseline. Repeated measures analyses will be used to identify any changes in outcomes from baseline to 12 months. Qualitative interviews will be transcribed verbatim. Inductive thematic analysis will be performed using NVivo software

(V.12, QSR International) to identify key themes, as guided by Braun and Clarke.³⁹

ETHICS AND DISSEMINATION

Ethics approval for this study has been granted by the St Vincent's Hospital (Sydney) Human Research Ethics Committee (HREC) (Project number 2021/ETH11847). Regulatory review approval has been granted by GenesisCare, and governance approval has been granted by the Edith Cowan University HREC (2022-03326-DALLAVIA).

Results of both the primary study and substudy will be reported in peer-reviewed academic journals, irrespective of the results observed. The results will also be presented at scientific meetings and conferences, as well as clinical forums and to other relevant health professionals and stakeholders.

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Contributors NS and YZ conceptualised the primary study. JDV, MK, SKR and JRL conceptualised the substudy. JDV, NS, MK, DAC, PP, JT, JM, SKR, JRL and YZ contributed to the development of the study design and methodology. JDV and NS contributed to drafting the manuscript. JDV, NS, MK, DAC, PP, JT, JM, SKR, JRL and YZ critically reviewed the draft, and have read and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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