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# BMJ Open Exercise during Chemotherapy for Ovarian cancer (ECHO) trial: design and implementation of a randomised controlled trial

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## ABSTRACT

**Introduction** Epidemiological evidence supports an association between higher levels of physical activity and improved cancer survival. Trial evidence is now needed to demonstrate the effect of exercise in a clinical setting. The Exercise during Chemotherapy for Ovarian cancer (ECHO) trial is a phase III, randomised controlled trial, designed to determine the effect of exercise on progression-free survival and physical well-being for patients receiving first-line chemotherapy for ovarian cancer.

**Methods and analysis** Participants (target sample size: n=500) include women with newly diagnosed primary ovarian cancer, scheduled to receive first-line chemotherapy. Consenting participants are randomly allocated (1:1) to either the *exercise intervention* (plus usual care) or *usual care* alone, with stratification for recruitment site, age, stage of disease and chemotherapy delivery (neoadjuvant vs adjuvant). The exercise intervention involves individualised exercise prescription with a weekly target of 150 minutes of moderate-intensity, mixed-mode exercise (equivalent to 450 metabolic equivalent minutes per week), delivered for the duration of first-line chemotherapy through weekly telephone sessions with a trial-trained exercise professional. The primary outcomes are progression-free survival and physical well-being. Secondary outcomes include overall survival, physical function, body composition, quality of life, fatigue, sleep, lymphoedema, anxiety, depression, chemotherapy completion rate, chemotherapy-related adverse events, physical activity levels and healthcare usage.

**Ethics and dissemination** Ethics approval for the ECHO trial (2019/ETH08923) was granted by the Sydney Local Health District Ethics Review Committee (Royal Prince Alfred Zone) on 21 November 2014. Subsequent approvals were granted for an additional 11 sites across Queensland, New South Wales, Victoria and the Australian Capital Territory. Findings from the ECHO trial are planned to be disseminated via peer-reviewed publications and international exercise and oncology conferences.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Randomised controlled study design.
- ⇒ Evaluation of exercise therapy delivered using an equitable mode of delivery, that is, telehealth delivery that is accessible to all.
- ⇒ Focus on a cancer type (specifically, ovarian cancer) that is understudied and under-represented in exercise oncology trials to date.
- ⇒ Adequately powered evaluation of practice-changing outcomes including progression-free survival, cost-effectiveness and chemotherapy adherence.
- ⇒ At the time of study design, it was unclear whether women receiving chemotherapy for newly diagnosed ovarian cancer could safely meet exercise prescription targets and the extent to which exercise dose completed would influence exercise effect.

**Trial registration number** Australian New Zealand Clinical Trial Registry (ANZCTR12614001311640; <https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=367123&isReview=true>).

## INTRODUCTION

The benefits of exercise for people with cancer, both during and following treatment, have been extensively investigated.<sup>1 2</sup> Consistently, high-quality evidence supports the beneficial impact of exercise on a wide range of physical, psychosocial and emotional health outcomes, but particularly for physical function, health-related quality of life, fatigue, anxiety and depression.<sup>1</sup> Epidemiological evidence also supports a positive association between physical activity and survival outcomes. Specifically, findings from a meta-analysis including mostly data from



observational studies found that risk of cancer-specific and all-cause mortality was 58% and 63% lower, respectively, for those in the highest category of physical activity post-cancer compared with those in the lowest physical activity category.<sup>3</sup> Further, exploratory findings from two randomised controlled trials involving patients with breast cancer have also shown a positive effect of exercise on survival outcomes.<sup>4,5</sup>

The compelling evidence base supporting the role of exercise in improving the quality, and potentially quantity, of cancer survivorship has been used to develop internationally endorsed guidelines.<sup>1,2,6</sup> These guidelines recommend that cancer survivors participate in 150 min per week of moderate-intensity, mixed-mode (aerobic and resistance) exercise. Yet, neither the scientific evidence nor the availability and promotion of these guidelines have enacted widespread integration of exercise therapy into cancer care globally or within any given country. Lack of workforce capacity, access to exercise oncology services and referral pathways, as well as associated costs (and lack of public reimbursement), have all been proposed as reasons preventing advancements in cancer care through exercise.<sup>7</sup> However, there also remain significant evidence gaps that cannot be ignored.

The current exercise oncology evidence base is largely derived from trials involving cancer types associated with good prognosis. Specifically, 89% of trials conducted to date involve cancers with 5-year survival rates that are higher than the 5-year survival rate for all cancers combined.<sup>8,9</sup> There is also a participant bias likely present in the majority of exercise trials, whereby participants tend to be younger, and have fewer comorbidities and a history of exercise participation, than the population from which they are drawn.<sup>10,11</sup> Consequently, the generalisability of findings to the wider population with cancer is unclear.<sup>10</sup> Additionally, approximately two-thirds of the interventions evaluated in exercise oncology trials are highly supervised, conducted in a gymnasium or clinic setting, and/or involve weekly exercise targets that do not align with current guidelines (eg, involve aerobic exercise only).<sup>8</sup> The dearth of evaluation of pragmatic, translational interventions limits the external validity and transferability of findings into standard practice. Further, adequately powered clinical trials evaluating the effect of exercise on survival, cost-effectiveness and adherence to standard oncology treatment are also lacking, yet it is precisely this evidence that is needed to promote equitable and widespread uptake of exercise into standard cancer care.

Unlike those diagnosed with common solid cancers, patients with ovarian cancer are more likely diagnosed with advanced stage disease and can expect poorer prognosis.<sup>12–15</sup> Ovarian cancer treatment typically involves extensive abdominal surgery and combination chemotherapy,<sup>13,16</sup> which is associated with acute and persistent side effects that lead to morbidity and declines in quality of life, driven by declines in physical well-being.<sup>17–20</sup> A population-based ovarian cancer study demonstrated

that only 32% of patients who were prescribed chemotherapy completed their regimen without dose reductions or delays.<sup>13</sup> Completion of the full chemotherapy dose is associated with longer survival, while delays, dose reductions and early cessation are associated with poorer outcomes.<sup>16,21</sup> The current 5-year ovarian cancer survival rate is 48%, which remains lower than the 5-year survival rate achieved in 1975 for all cancers combined.<sup>22</sup>

Data collected from prospective, longitudinal cohort studies show low and decreasing levels of physical activity following diagnosis of ovarian cancer for the majority (up to 80%<sup>23,24</sup>), and that lower physical activity levels were associated with reduced quality of life and chemotherapy completion.<sup>25</sup> As such, patients with ovarian cancer arguably represent a group with the most to gain through exercise, yet they also represent one of the least studied cancer cohorts in exercise oncology trials. Findings from a 2020 systematic review which included data from five studies (one randomised controlled trial and four pre/post-trials) evaluating the effect of an exercise intervention in women with ovarian cancer provide preliminary evidence supporting exercise as being safe and feasible, and may lead to benefits in health-related quality of life, fatigue, physical and mental function, strength, sleep and chemotherapy completion rates.<sup>26</sup> There is a clear need for further research that seeks to reduce morbidity and improve quality of life and survival following ovarian cancer, and exercise intervention has potential for benefit.

The Exercise during CHemotherapy for Ovarian cancer (ECHO) trial is a randomised controlled clinical trial evaluating the value of physical exercise during chemotherapy for patients with newly diagnosed ovarian cancer. We hypothesise that compared with usual care, exercise therapy during chemotherapy will result in improved progression-free survival and higher scores for physical well-being at 6 and 12 months post-randomisation, and lower morbidity and more efficient use of healthcare resources compared with usual care.

## METHODS AND ANALYSIS

This manuscript was written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines<sup>27</sup> (SPIRIT checklist provided in online supplemental file 1). Ethics approval was granted by the Sydney Local Health District Ethics Review Committee (2019/ETH08923), approved on 21 November 2014 (online supplemental file 2). This trial was registered with the Australian New Zealand Clinical Trial Registry (ANZCTR12614001311640). The approved study protocol, and the participant information and consent form can be found in online supplemental files 3 and 4, respectively.

The ECHO trial is a national, multicentre, phase III randomised controlled trial being conducted in collaboration with the National Health and Medical Research Council Clinical Trials Centre (NHMRC CTC) and the

**Table 1** Eligibility criteria for participation in the ECHO trial

**A patient is eligible if they meet:**
**All the following:**

- ▶ Newly diagnosed epithelial ovarian, primary peritoneal or fallopian tube cancer of any histological subtype, suitable for first-line chemotherapy.
- ▶ Age  $\geq 18$  years.
- ▶ ECOG status 0–2.
- ▶ Willing and able to comply with all trial requirements, including the exercise intervention, timing and/or nature of required assessments.
- ▶ Sufficiently fluent in English to fully participate in data collection requirements and comprehend intervention requirements.
- ▶ Scheduled for chemotherapy or has commenced chemotherapy. Participants must be enrolled prior to commencement of the second cycle of chemotherapy.
- ▶ Signed written informed consent.

**None of the following:**

- ▶ A diagnosis of recurrent ovarian cancer.
- ▶ History of another malignancy within 3 years prior to registration (excluding adequately treated carcinoma in situ, basal cell or squamous cell carcinoma of the skin, stage I melanoma in situ or superficial transitional cell carcinoma of the bladder). Patients with a history of other malignancies are eligible if they have been continuously disease free for at least 3 years after definitive primary treatment.
- ▶ Concurrent illness (including severe infection or unstable angina) that may jeopardise the ability of the patient to undergo the exercise intervention outlined in this protocol with reasonable safety.
- ▶ Serious medical or psychiatric conditions that might limit the ability of the patients to comply with the protocol.

ECHO, Exercise during CHemotherapy for Ovarian cancer; ECOG, Eastern Cooperative Oncology Group.

Australia New Zealand Gynaecological Oncology Group. The ECHO trial aims to evaluate the enduring effects of an individualised, telehealth-delivered exercise intervention (plus usual care) versus usual care alone, during first-line chemotherapy for patients with ovarian cancer.

### Patient and public involvement

Consumer representatives (authors HO, MW) are embedded within the ECHO trial. They have been involved in all stages of trial development, funding submissions and study implementation. Specifically, our consumers provided perspectives on study design, chosen outcome of interests, timing and duration of the intervention, delivery mode of intervention, and have reviewed and edited all participant-facing study documentation to minimise participant burden. Further, involvement of our consumers throughout the implementation phase continues via participation in teleconference meetings, and our consumers will lead dissemination of trial findings to consumer groups.

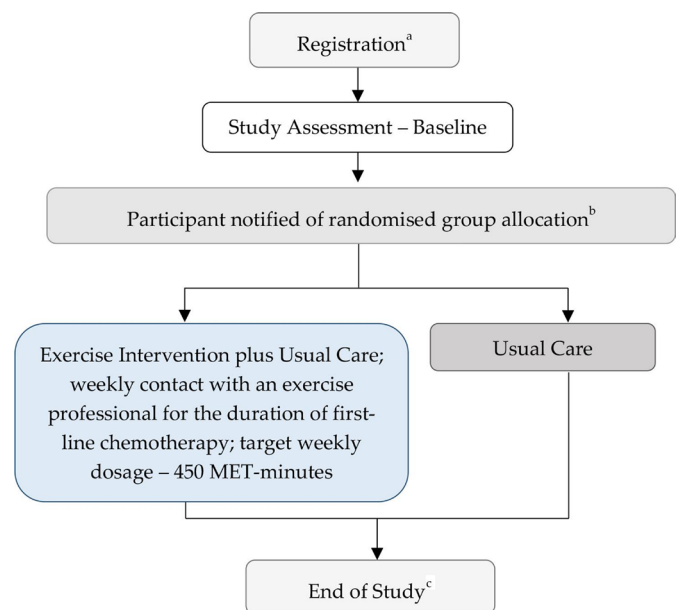
### Eligibility criteria/participants

To be eligible, participants are required to meet all the inclusion criteria and none of the exclusion criteria presented in table 1.

### Recruitment, registration and randomisation

Participating sites along with their relevant ethical approvals granted are shown in online supplemental table 1 and participant flow is shown in figure 1. Potentially eligible patients are identified by clinical trial nurses, or directly referred to Griffith University by their treating gynaecological/medical oncologist. The trial is introduced and discussed with potentially eligible patients, thereafter providing patients with the participant information and consent forms, confirming eligibility status,

and collecting written informed consent for all interested and eligible patients. Consenting patients are registered into a centrally administered database and randomised 1:1 to the *exercise intervention* (exercise intervention plus



**Figure 1** Participant flow through the Exercise during CHemotherapy for Ovarian cancer trial. <sup>a</sup>Registration includes randomisation with stratification for recruitment site, age (<70 vs  $\geq 70$  years), stage of disease (I–II vs III–IV) and chemotherapy delivery (adjuvant vs neoadjuvant plus adjuvant). Staff involved with baseline assessments and participants remain blinded to randomisation outcome at this stage. <sup>b</sup>Staff involved with data collection remain blinded to randomisation outcome. <sup>c</sup>Progression status and survival status will be updated periodically throughout trial duration and at approximately 6 months prior to end of trial. MET, metabolic equivalent.

usual care) or *usual care* group using the Flextrials Enrollment System (computerised, password-protected randomisation system with the NHMRC CTC). Randomisation is stratified by recruitment site, age (<70 vs ≥70 years), International Federation of Gynecology and Obstetrics stage of disease (I–II vs III–IV) and chemotherapy delivery (adjuvant vs neoadjuvant plus adjuvant). Demographic, disease and treatment-related characteristics are extracted from medical records and entered into a centralised database (OpenClinica) via an electronic case report form. Newly recruited participants are contacted via telephone, to collect a full medical history (including comorbidities and medications) and schedule a baseline assessment.

### Blinding and bias

Group allocation is concealed from consenting patients until post-baseline assessment. The nature of exercise prevents the participant and exercise professionals delivering the intervention from being blinded to group allocation; however, all clinicians and research staff involved with recruitment, data extraction from medical records and data entry are blinded to group allocation. Research staff collecting objectively assessed outcomes are trained to follow a validated protocol and are blinded to treatment group and previous scores.

### Assessments and intervention timing

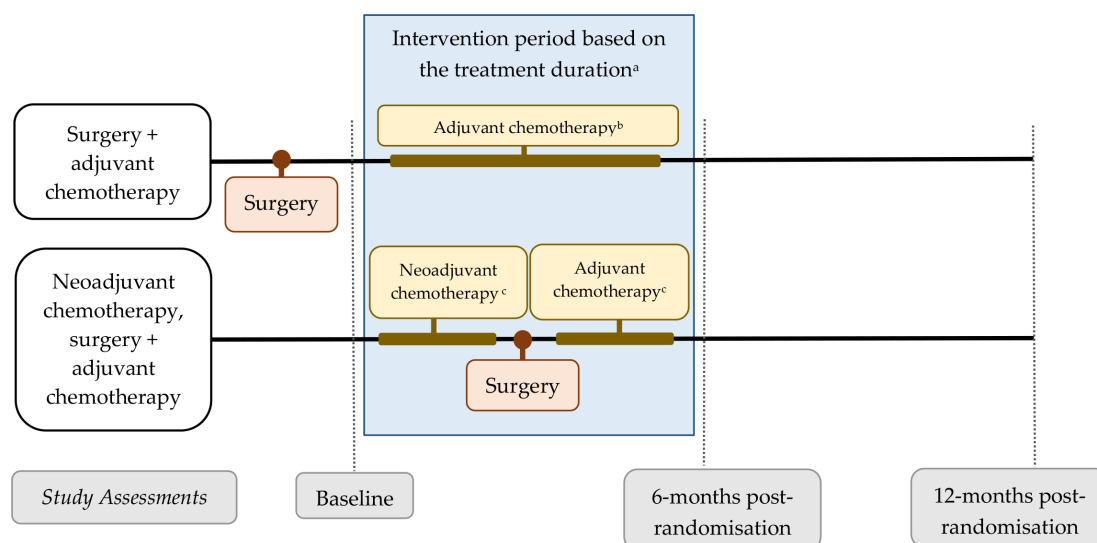
Assessments of participant-reported and objectively measured outcomes are conducted at baseline (prior to second cycle of chemotherapy), and at 6 and 12 months post-randomisation (figure 1 and online supplemental table 2). Assessments for objectively measured outcomes are conducted at a university-based or hospital-based clinic

or the participant's home. Data related to chemotherapy completion rate and chemotherapy-related adverse events are extracted from medical records post-baseline assessment and updated at 12 months post-randomisation. Participants who withdraw or stop the exercise intervention early continue completing follow-up assessments, if they agree to do so.

Following baseline assessment, each participant receives a group allocation letter and an Ovarian Cancer Australia 'Resilience Pack'. The Resilience Kit contains information relating to the diagnosis and treatment of ovarian cancer, support services and staying well (including through physical activity).<sup>28</sup> Those in the exercise group are also assigned an exercise oncology professional (ExP) and are mailed intervention materials, including an exercise tracker and a Borg Rating of Perceived Exertion Scale. Participants in the exercise group are then contacted by their allocated ExP and begin the intervention within 7 days of baseline assessment. The exercise intervention is designed to span the duration of first-line chemotherapy, which is typically scheduled over an 18-week period, but may be longer to accommodate interruptions (eg, surgery for those who have had neoadjuvant chemotherapy) or dose delays (figure 2). Should chemotherapy cease earlier due to disease progression, shorter planned chemotherapy or any other reason, continued access to the intervention as appropriate and desired by the participant, up to a maximum of 18 weeks (from commencement of intervention), is provided.

### Outcomes and timing of assessment

Outlined in table 2 are the outcomes of interest, methods and timing of assessment, and a priori defined clinically



**Figure 2** Trial assessment schedule and timing of intervention for women who receive surgery plus adjuvant chemotherapy versus women who receive neoadjuvant chemotherapy, surgery plus adjuvant chemotherapy. <sup>a</sup>Participant may commence chemotherapy prior to intervention commencement (intervention commencement is anchored to baseline assessment). Intervention may continue beyond 6 months post-randomisation assessment if treatment delays occur. <sup>b</sup>Typically six cycles of chemotherapy scheduled over 18 weeks. <sup>c</sup>Typically three cycles of neoadjuvant chemotherapy scheduled over 9 weeks, followed by three cycles of adjuvant chemotherapy scheduled over 9 weeks.

**Table 2** Trial outcomes, methods of assessment, clinically relevant effect size\* and timing of assessment

Outcomes of interest, assessments and clinically relevant effect (CRE) size	Time point			
	B	6m	12m	Y†
<b>Primary outcomes</b>				
<i>Progression-free survival</i>				
As determined by the responsible clinician, according to pragmatic clinical criteria including imaging, serum Ca125 levels and/or commencement of further anti-cancer treatments. <sup>42 43</sup> CRE: 25% reduction in hazard rate. <sup>40</sup>			X	X
<i>Physical well-being</i>				
Physical well-being subscale of the FACT-O (range=0–28); CRE: 2 units. <sup>44 45</sup>	X	X	X	
<b>Secondary outcomes</b>				
<i>Overall survival</i>				
Date of death abstracted from medical records or death registry; CRE: 25% reduction in the hazard rate. <sup>40</sup>			X	X
<i>Physical function</i>				
<u>Objectively measured outcomes</u>				
Fitness—Six-Minute Walk Test; CRE: ≥50-metre increase. <sup>46 47</sup>	X	X	X	
Upper-body muscular endurance—YMCA Bench Press; CRE: 0.5 SD. <sup>48 49</sup>				
Lower-body muscular endurance—30-second Sit to Stand; CRE: 2 repetitions. <sup>50</sup>				
Balance—Single Leg Stance (eyes closed); CRE: 0.5 SD. <sup>48 49</sup>				
<u>Participant-reported outcome</u>				
Short Form Health Survey; CRE: 0.5 SD. <sup>51</sup>				
<i>Body composition</i>				
Fat mass and fat-free mass as measured by bioimpedance spectroscopy; CRE: relative improvement of 5%. <sup>52 53</sup>	X	X	X	
Lymphoedema status as measured by bioimpedance spectroscopy; CRE: 5% absolute difference in % with evidence of lymphoedema between groups. <sup>54 55</sup>				
<i>Quality of life</i>				
FACT-O (range=0–156); CRE: 8 units. <sup>45</sup>	X	X	X	
Measure of Ovarian Symptoms and Treatment Concerns <sup>41 56</sup> ; CRE: 0.5 SD. <sup>48 49</sup>				
PROMIS—Global Health <sup>57</sup> ; CRE: 0.5 SD. <sup>48 49</sup>				
EQ-5D (range=0–1) <sup>58</sup> ; CRE: 0.06. <sup>59</sup>				
<i>Fatigue</i>				
Functional Assessment of Chronic Illness Therapy—Fatigue; CRE: 3 units. <sup>60</sup>	X	X	X	
<i>Sleep</i>				
Insomnia Severity Index; CRE: 6 units. <sup>61</sup>	X	X	X	
Pittsburgh Sleep Quality Index; CRE: 3 units. <sup>62</sup>				
<i>Anxiety and depression</i>				
Hospital and Anxiety Depression Scale; CRE: 1.5 units. <sup>63</sup>	X	X	X	
<i>Chemotherapy completion rate</i>				
Relative dose intensity (RDI) of each agent (total delivered dose/week) as a % of the initial target dose (standard dose intensity calculated for each regimen by summing RDI for each agent given when calculating average). CRE: 5% absolute difference between groups. <sup>64</sup>		X		
<i>Chemotherapy-related adverse events (AEs)</i>				
Proportion of grade 3/4 AEs related to treatment of ovarian cancer as measured by the standard CTC-AE V.4 and recorded in medical records <sup>65</sup> ; CRE: 0.5 SD. <sup>48 49</sup>	X	X†	X	
FACT-O Trial Outcome Index (range=0–72); CRE: 4 units. <sup>44</sup>				
<i>Healthcare use</i>				
Healthcare usage data will be obtained from study clinical records and Services Australia (Medicare) claims. These will include treatments, appointments/tests, AEs and hospitalisation. Costs will be assigned to hospitalisation using national cost schedules (eg, AR-DRGs). Resources for implementing the intervention will be recorded by the trial managers. Costs to patients (lost employment and out-of-pocket costs including exercise-related costs) will be assessed using validated questions developed for populations with cancer. <sup>66 67</sup>			X	

Continued



Table 2 Continued

Outcomes of interest, assessments and clinically relevant effect (CRE) size	Time point			
	B	6m	12m	Y†
<b>Tertiary outcomes</b>				
<i>Biomarkers</i>				
Serum (plain blood collection tube), plasma (EDTA blood collection tube) and whole blood (Paxgene).	X	X	X	
*In the absence of established cut-offs, clinically important changes were defined as 0.5 SD difference between follow-up and baseline measures. <sup>48 49</sup>				
†At approximately the 4.5-year mark of the trial timeline.				
‡Data related to chemotherapy completion rate and chemotherapy-related AEs are extracted from medical records monthly across the chemotherapy period per participant.				
AR-DRGs, Australian Refined Diagnosis Related Groups; B, baseline; CTC-AE, Common Terminology Criteria for Adverse Events; EQ-5D, EuroQol 5-Dimension; FACT-O, Functional Assessment of Cancer Therapy-Ovarian; 6m, 6 months post-randomisation; 12m, 12 months post-randomisation; PROMIS, Patient-Reported Outcomes Measurement Information System; Y, yearly thereafter.				

relevant thresholds. Progression-free survival and physical well-being are the primary outcomes. Progression-free survival has been recommended as an appropriate survival endpoint for first-line trials in ovarian cancer, provided that the intervention is not overly toxic and that important secondary endpoints are also assessed (including overall survival, patient-reported outcomes, severity of adverse effects and economic evaluation), as is the case for the ECHO trial.<sup>29</sup> The advantages of progression-free survival as the primary endpoint (compared with overall survival) include an earlier and more sensitive signal of anti-tumour efficacy, a lower likelihood of influence by competing risks (particularly relevant for older participants) and reduced chance of confounding from treatments received after progression.<sup>30–34</sup> Improving progression-free survival is also a direct, tangible and important benefit to patients, as it delays cancer-related symptoms and side effects of second-line treatment.<sup>35</sup> Physical well-being was also chosen as a primary outcome as chemotherapy-related side effects contribute to declines in physical well-being, which in turn drive declines in overall quality of life.<sup>17–20</sup> Further, there is strong evidence from trials outside of the ovarian cancer setting, as well as from pilot work undertaken in preparation for the ECHO trial, that demonstrate exercise during chemotherapy can improve physical well-being.<sup>1 36</sup> Secondary outcomes (listed in table 2) include outcomes that matter to the patient and their clinicians, are lacking in level 1 evidence beyond common cancer types and are significant determinants of subsequent uptake of exercise in routine clinical practice. A more detailed description of the methods of assessment for each outcome can be found in online supplemental table 3. Participants are also invited to provide blood samples for future exploratory analyses of biomarkers that are potentially prognostic and/or predictive of a response to exercise. Questionnaires and trial assessment forms (used to record objectively assessed outcome data) are scanned and imported into the trial database at the NHMRC CTC.

### Exercise intervention

The exercise intervention (online supplemental table 4) is delivered by tertiary (minimum 3-year undergraduate training in exercise science or physiotherapy) and trial-trained ExP for the duration of first-line chemotherapy. The weekly intervention target is to accumulate at least 150 min per week of moderate-intensity, mixed-mode (aerobic and resistance-based) exercise, with participants encouraged to complete at least two resistance-based exercise sessions per week.<sup>1 2 6</sup> This is equivalent to an exercise dosage of 450 metabolic equivalent minutes per week. The starting exercise dosage (and parameters comprising dosage: frequency, intensity, duration and type) and pace of progression to this weekly target are individualised according to each participant's circumstance. Progression may occur through modification of duration and number of sessions per day, mode and/or intensity.

The intervention is delivered via weekly telephone sessions with an ExP. Patients experiencing difficulty adhering to the prescribed weekly exercise dosage are offered more frequent telehealth sessions. Less frequent contact may occur for those with high exercise self-efficacy, typically meeting the weekly exercise target and who are equipped to accommodate exercise barriers appropriately, that is, for whom weekly contact is therefore unnecessary or burdensome. When possible and when participants approve, the telehealth intervention is supported by five face-to-face visits with an ExP (either trial trained or an accredited exercise physiologist or physiotherapist) scheduled throughout the intervention. This intervention feature aligns with Australia's Chronic Disease Management Plan, which allows for up to five reimbursable visits per year with an allied health professional.

The ExP uses a patient-centred approach in the delivery of the intervention by following the Chronic Disease Self-management Intervention Model (CDSM), adapted from our previous work in breast cancer.<sup>37</sup> The

**Table 3** Educational topics covered during the ECHO trial exercise intervention

Topics	
What to expect during the exercise intervention	Exercise frequency
Exercise and treatment side effects	Exercise intensity
Why should I be active?	Exercise session components
When not to exercise	Goal setting
Being active safely	Motivation and support
What and how much should I do?	Identify and problem-solve barriers
Starting and progressing	Getting back on track after an interruption to exercise
Types of exercise	Exercise after the intervention
Frequency, Intensity, Time and Type	
ECHO, Exercise during CHemotherapy for Ovarian cancer.	

CDSM emphasises collaborative interactions with the ExP providing education, support and exercise prescription guidance according to each patient's individual circumstances (considering health history, previous exercise behaviours, diagnosis and treatment characteristics, and treatment-related side effects), while concurrently acknowledging the participant's expertise in knowing what works best in the context of their life and their effort versus reward willingness and expectations. Each session involves (1) an assessment of the previous week's completed exercise, barriers to exercise, changes to medications or chemotherapy, presence and change to treatment-related side effects (and review of potential relationship with exercise) and details related to the occurrence of any exercise-related adverse event; (2) provision of advice including exercise prescription for the coming week and recommendations for exercise modifications in response to treatment-related side effects or exercise-related adverse events if relevant, as well as provision of education on exercise topics (table 3); and (3) assistance relating to overcoming barriers (including treatment-related side effects) or dealing with exercise-related adverse events. Over the course of the intervention, the goal for the ExP is to develop independent, regular exercisers, capable of achieving and adhering to the weekly exercise target beyond the duration of the intervention without regular ExP support. Further, ExPs are instructed to remain within their scope of practice during sessions with participants, and to refer patients back to their treating team if unmanaged disease-related or treatment-related side effects present.

A trial-specific case management folder (CMF) is maintained by the ExPs for each participant to facilitate comprehensive recording of intervention delivery and

adherence, exercise compliance and the occurrence of exercise-related adverse events. The CMF provides a record of: contacts (dates, mode (telephone, face-to-face, texts, emails or video conferencing) and duration of contact); education topics covered (see table 3) and when; voluntary purchases made by the participant related to participating in the trial; detailed notes related to the 'assess, advise and assist' components of the CDSM; exercise dosage prescribed and dose completed each week through recording daily exercise mode (including number and type of exercises for resistance exercise and specific mode of aerobic exercise), duration and intensity (according to 0–10 Rating of Perceived Exertion Scale)<sup>38 39</sup>; and exercise-related adverse events including type, grade, causality (relationship to the intervention) and impact (eg, hospitalisation required and/or impact to intervention). Completed CMFs are reviewed for completeness and assessment of intervention fidelity by the senior trial ExP, are used to facilitate case discussions at monthly trial ExP meetings and will be used to quantify intervention safety and feasibility. Each exercise group participant is provided with an exercise logbook, which they are advised to use to record prescribed and completed exercise throughout the intervention.

### Usual care

Participants in the usual care group may be provided with physical activity advice during and after treatment from members of their treating team or may access physical activity advice from other sources (eg, Ovarian Cancer Australia's Resilience Kit, cancer organisations, private accredited exercise physiologists, etc). Therefore, participation in this trial does not preclude patients in the usual care group from exercising regularly; however, exercise participation is neither assessed nor monitored throughout their chemotherapy.

### Sample size justification

A total accrual of approximately 500 participants recruited over 6 years, with an additional follow-up of 2 years, provides over 80% power to detect a difference of 6.7 months in median progression-free survival, assuming a median progression-free survival in the usual care group of 20 months (HR: 0.75, 400 observed progression-free survival events), with a two-sided type 1 error rate of 0.045. This includes overaccrual of approximately 26 participants to account for ineligibility, withdrawal prior to baseline assessment and missing data. This degree of progression-free survival improvement is similar or greater than those seen in pivotal trials of expensive and targeted therapies in ovarian cancer, which have been translated into routine clinical practice and reimbursement by regulatory authorities.<sup>40 41</sup>

Approximately 210 participants per group also provide 80% power to detect an absolute minimum clinically important difference of 2 points between the mean physical well-being scores of the groups at 6 and 12 months post-randomisation, assuming an SD of 5.6, a two-sided



type 1 error rate of 0.005, with an allowance of approximately 15% for missing data.

### Statistical methods and analysis

Efficacy analyses will be by intention-to-treat including all randomised participants. The presence of baseline group imbalances in outcomes and potential confounders, although not expected, will be explored for potential adjustment in sensitivity analyses. Attrition and contamination in both groups will be tracked with validated physical activity instruments completed at each assessment. Kaplan-Meier curves will be used to describe progression-free and overall survival and the log-rank test will be used to test for differences between treatment and usual care groups. Provided relevant assumptions are met, physical well-being and the secondary outcomes will be analysed using Generalised Estimating Equations, accounting for correlations between repeated measurements in the same subject, and allowing examination of partially complete records, to test the effects of treatment group and time. Effects of treatment (eg, HRs, differences in mean patient-reported outcomes, ORs), with appropriate 95% CIs, will be used to describe the effects of exercise. We will undertake a within-trial cost-utility analysis and compare the costs and quality-adjusted life years (QALYs) for the treatment and usual care groups to produce an incremental cost per QALY ratio. Cost-utility analysis will employ non-parametric bootstrapping statistics using the bias-corrected approach. One-way and probabilistic sensitivity analyses will be used to address data uncertainty and identify scenarios which produce value for money.

### Trial management

The Trial Management Committee (TMC) oversees trial planning, monitoring, progress, review of information from related research and implementation of recommendations from other trial committees and external bodies (eg, ethics committees). The TMC meets two to four times per year and considers whether to continue the trial as planned, modify or stop it, based on available information.

### ETHICS AND DISSEMINATION

Written informed consent was provided by all participants after eligibility was established and prior to baseline assessment. The trial was conducted according to the guidelines of the Declaration of Helsinki and approved by the Sydney Local Health District Ethics Review Committee (2019/ETH08923), 21 November 2014).

The ECHO trial aims to recruit a representative sample of patients newly diagnosed with ovarian cancer, who are on average, insufficiently active at diagnosis. The first ECHO participant was recruited on 30 June 2015 and we anticipate achieving our recruitment target in the first quarter of 2023. The evidence-based exercise intervention is delivered via telehealth, facilitating equitable access for all patients, including patients who live in

more rural, regional areas of Australia. Further, the trial is adequately powered to evaluate survival, alongside a range of outcomes that matter to patients with ovarian cancer and their multidisciplinary team. As such, positive trial findings have significant potential to accelerate improvements in survival and well-being not just for patients with ovarian cancer, but for the broader population with cancer. It is possible that on trial completion, the null hypothesis will be accepted. An insufficient or unfeasible weekly exercise dosage, too short intervention or simply that exercise is unable to shift survival outcomes for patients with ovarian cancer all represent plausible reasons for null findings. However, the ECHO sample size, alongside the comprehensive data collection protocol for exercise safety and feasibility, will allow for in-depth exploration of the relationship between exercise dose and outcomes and whether this relationship is mediated by patient, diagnosis, treatment and behavioural characteristics. The collection of blood samples will also provide rich samples for the subsequent analysis of potential biological mechanisms through which exercise may benefit. In addition, the feasibility data will be used to assess and describe what exercise patients are willing, able and interested in doing in endeavours to improve survival and/or quality of life outcomes. However, should the null hypothesis be rejected, the ECHO trial findings are poised to force policy change, and to fundamentally shift patient and clinician perceptions about the need for exercise therapy in cancer care.

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