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Alpe d'HuZes Cancer Rehabilitation (A-CaRe) Research: Four Randomized Controlled Exercise Trials and Economic Evaluations in Cancer Patients and Survivors

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Abstract
Background Previous studies showed that exercise in cancer patients is feasible and may reduce fatigue and improve physical fitness and quality of life. However, many previous studies had methodological weaknesses related to trial design, sample size, comparison group, outcome measures, short follow-up durations and programme content.

Purpose This paper aims to present the rationale and design of the clinical research subprogramme of the Alpe d'HuZes Cancer Rehabilitation (A-CaRe) programme.
Method A-CaRe Clinical Research includes four randomized controlled trials in patients: (a) after chemotherapy, (b) during chemotherapy, (c) after stem cell transplantation and (d) during childhood cancer. These trials compare high-intensity

Laurien Buffart and Mai Chinapaw share first authorship since they have equally contributed to this manuscript.

Trial registration This study is registered at the Netherlands Trial Register: NTR2153 (study 1), NTR2159 (study 2), NTR2341 (study 3) and NTR1531 (study 4).

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resistance and endurance exercise interventions with usual care or a waiting list control group. In two studies, a second intervention arm consisting of low-to-moderate intensity exercise is included. All four A-CaRe trials use similar methods.

Results Outcome measures are carefully chosen based on the International Classification of Functioning Disability and Health model. Measurements will be performed prior to randomization (T0), after completion of the intervention (T1) and at follow-up (T2). The primary outcome measures are cardiorespiratory fitness, muscle strength and fatigue. Secondary outcome measures include health-related quality of life and psychosocial functioning. Furthermore, cost-effectiveness and cost-utility analyses are performed from a societal perspective.

Conclusion We hypothesize that exercise is more effective at improving physical fitness and thereby reducing fatigue and more cost-effective compared with usual care or a waiting list control group. If so, the programmes will be implemented in the Dutch clinical practice.

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Keywords Exercise · Cancer · Rehabilitation · Physical fitness · Muscle strength · Fatigue

Abbreviations

A-CaRe	Alpe d'HuZes Cancer Rehabilitation
HRQoL	Health-related quality of life
peakVO_2	Peak oxygen uptake
RCT	Randomized controlled trial

Introduction

Recent advances in diagnosis and treatment of cancer patients have led to improved survival rates, both for children and adults. In The Netherlands, the current 5-year survival rate across all cancers is approximately 62% for female and 56% for male patients [1]. The survival rates of childhood cancer have improved up to 75% [2, 3]. However, cancer treatment and survival are often associated with prolonged psychosocial and physical complaints [4, 5], including decreased muscle strength, reduced lean body mass, reduced cardiorespiratory fitness, bone loss and fatigue [6]. For example, approximately 70% of cancer patients report fatigue complaints during chemotherapy and/or radiotherapy [7–9], and even years after the end of therapy, fatigue is still a major problem for at least 30% of cancer survivors [9]. Feelings of fatigue may result in the avoidance of activities to reduce the discomfort. However, this may result in a self-perpetuating condition of diminished activity leading to reduced physical fitness, increased muscle wasting and consequently to easy fatigue and further physical inactivity [6, 9]. This has great impact on the patient's quality of life [7, 9]. This is also true for survivors of childhood cancer [10]. Geenen et al. reported that 75% of childhood cancer survivors had at least one adverse health effect after a median follow-up of 17 years [11]. Late health effects include adverse general and mental health, activity limitations, functional impairments [2], reduced physical fitness, increased fatigue and reduced health-related quality of life (HRQoL) [12].

Several literature reviews summarized the available scientific literature on the effects of exercise interventions in adult cancer patients and survivors [4, 13–18]. These studies suggest that cancer patients may benefit from physical exercise both during and after treatment. The suggested beneficial effects include improved physical performance, self-reported functioning and psychological and social well-being, as well as reduced fatigue and increased quality of life [4, 13, 14, 16–18]. The majority of the studies focused on patients with breast cancer, and fewer studied colorectal, lung and prostate cancers [13, 15, 16]. A recent literature review of Liu et al. [15] reported

that physical exercise interventions were also feasible to conduct in haematological cancer patients and that results on physical fitness, HRQoL and psychological well-being were encouraging [15].

However, evidence of the beneficial effects of exercise in cancer patients and survivors appeared to be limited due to poor to moderate methodological quality of the studies. Most studies were not randomized controlled trials (RCTs), did not include appropriate control groups and/or were based on small sample sizes. Furthermore, most exercise interventions were sub-optimal regarding exercise physiological aspects: Exercise programmes were relatively short in duration (less than 12 weeks) and did not systematically promote maintenance of physical activity among the patients after the programme, and most studies included only low-intensity aerobic exercise, such as walking or cycling, rather than resistance exercise and high-intensity exercise [13, 16, 19]. Since muscle atrophy is a common problem in cancer patients [20], it seems advisable to include resistance exercises as well. With appropriate training stimuli, skeletal muscles can show great adaptability even in case of severe muscle atrophy and fatigue [6].

In The Netherlands, a cancer rehabilitation programme 'Recovery & Stability' [21, 22] exists. This is a 12-week supervised self-management exercise programme of low-to-moderate intensity that combines endurance and resistance exercises with group sports activities. The Recovery & Stability programme showed improvements in physical fitness [21] and quality of life [23], which sustained 9 months post-intervention [23], but the study did not include a no-exercise control group. Another cancer rehabilitation programme in The Netherlands included high-intensity resistance and endurance training after chemotherapy treatment and showed improved physical performance and quality of life in cancer patients compared with a historical control group [19]. These effects persisted at 1 year follow-up [24].

In summary, previous studies showed that exercise-based rehabilitation programmes of moderate or high intensity are feasible and well tolerated by adult cancer patients and survivors. However, RCTs including adequate sample sizes, an appropriate control group and valid and reliable outcome measures are limited. Furthermore, no studies have examined the cost-effectiveness of any type of exercise programme in cancer patients. Therefore, a cancer rehabilitation research programme was proposed to and approved by the Dutch Cancer Society, financed through this society by the so-called Alpe d'HuZes foundation (www.opgevenisgeenoptie.nl), a cancer research fund. This Alpe d'HuZes Cancer Rehabilitation (A-CaRe) programme includes a clinical research subprogramme (A-CaRe Clinical Research) in addition to subprogrammes aiming at patient empowerment and public relations. The primary objectives of A-CaRe Clinical Research are to evaluate the effectiveness of state-of-the-art exercise interventions with respect to physical fitness and fatigue and secondarily HRQoL in specific cancer patient and survivor groups and to evaluate the cost-effectiveness of these interventions. The present paper describes the design of the A-CaRe Clinical Research programme.

Methods

A-CaRe Clinical Research includes four RCTs with follow-up periods up to 1 year focusing on different subgroups: (a) exercise after chemotherapy [25], (b) exercise during chemotherapy [26], (c) exercise after stem cell transplantation [27] and (d) exercise during childhood cancer [28] (Table 1).

The design of the A-CaRe trials is based on a conceptual model, presented in Fig. 1. According to this model, exercise improves physical fitness (cardiorespiratory fitness and muscle strength), which improves fatigue and subsequently also physical function and HRQoL. Physical fitness may also directly influence physical function and HRQoL.

In the A-CaRe trials, exercise interventions will be compared with either a waiting list control group or usual care. All four A-CaRe trials will use similar methods.

Study Population

Potentially eligible patients will be screened by the treating physician for the presence of comorbid conditions that would contraindicate participation in a physical exercise programme. This includes patients who are wheelchair dependent or not able to perform basic physical activities like walking or cycling, patients with contraindications for physical activity or exercise (i.e. serious orthopaedic conditions that would hamper functional recovery, serious cardiovascular or cardiopulmonary risks), patients with serious psychiatric or cognitive problems or severe emotional instability, patients suffering from malnutrition (evidenced by an unintended weight loss of more than 5% per month or more than 10% unintended weight loss during the previous 6 months), patients not being familiar with the Dutch language, patients who are unable to follow exercise instructions and patients participating in concurrent studies or rehabilitation programmes containing physical activity or exercise. Due to the focus on different patient populations, each A-CaRe study has its own inclusion criteria. Table 2 presents the inclusion criteria for each RCT, as well as additional trial-specific exclusion criteria.

Exercise Interventions

Table 1 presents the intervention and control arms of all four A-CaRe trials. In general, the exercise interventions

Table 1 Intervention and control arms of the A-CaRe trials

	1. Exercise after chemotherapy	2. Exercise during chemotherapy	3. Exercise after SCT	4. Exercise during childhood cancer
Intervention duration	12 weeks	Depending on duration of chemotherapy	18 weeks	12 weeks
Intervention arm 1	High-intensity resistance and endurance exercise	High-intensity resistance and endurance exercise	High-intensity resistance and endurance exercise	High-intensity resistance and endurance exercise
Intervention arm 2	Low-to-moderate intensity resistance and endurance exercise	Low-to-moderate intensity physical activity programme	–	–
Control arm	Waiting list[a]	Usual care	Usual care[b]	Usual care

SCT stem cell transplantation

[a] After 12 weeks, patients will start with the high-intensity resistance and endurance programme or the light-to-moderate intensity exercise programme, depending on which programme they have been allocated to

[b] Currently, 10–20% of patients after SCT participate in the Recovery & Stability programme, in most cases starting 6 months or longer after transplantation

consist of high-intensity resistance and endurance exercises under supervision of a physical therapist twice a week, with a duration of 60 min. Furthermore, all interventions include a behavioural motivation component aimed at increasing motivation and compliance to physical exercise. Patients who completed treatment trained for 12 weeks. The Recovery & Stability programme showed that an intervention duration of 12 weeks was sufficient to achieve beneficial effects on physical fitness and HRQoL [21]. Also De Backer et al. [19] showed the largest improvements in physical fitness to occur in the first 12 weeks training. However, patients after stem cell transplantation who are treated more aggressively are at increased risk for persistent complaints [29]; they are more likely to have lower levels of physical fitness and higher levels of fatigue and consequently may need more time to recover. Therefore, for these patients, the intervention duration was extended to 18 weeks.

In general, the high-intensity resistance programme will consist of exercises targeting the large muscle groups of the upper and lower extremities. Resistance exercises are performed at 65% to 80% of the one repetition maximum (1-RM), consisting of two sets of 10–15 repetitions. Every 4 weeks, the training progress is evaluated by means of an indirect 1-RM test, and the training intensity is adjusted accordingly.

The high-intensity endurance exercises are performed at an intensity of 65% of the maximal workload of the steep ramp test [30]. This corresponds to a score of 15 on the Borg scale for ratings of perceived exertion [31]. Endurance exercises are mainly performed on a cycle ergometer. Additionally, other modes of endurance, such as rowing, will be used depending on the patients' preferences.

A behavioural motivation component is included to improve compliance and stimulate physical activity outside the exercise programme. Patients are encouraged to be moderately physically active for at least 30 min, three times per week in addition to the supervised programme. After completion of the exercise intervention, patients are encouraged to be moderately physically active for at least 30 min five times per week. Specific programme elements include the provision of general and motivational information, both

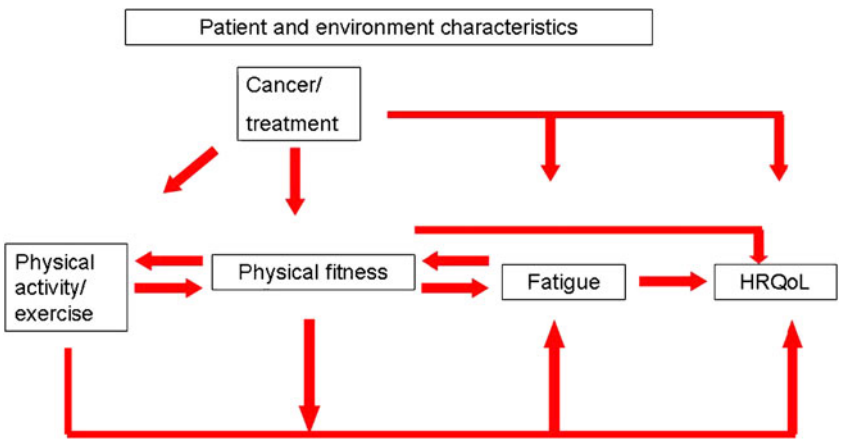

Fig. 1 Conceptual model of the A-CaRe trials

Table 2 Number of patients, participating hospitals and in- and exclusion criteria of the A-CaRe trials

Project	# of patients	Inclusion criteria	Specific exclusion criteria[a]	Participating hospitals
1. Exercise after chemotherapy	400	Histological confirmed breast, colon, ovarian cancer or lymphomas with no indication of recurrent or progressive disease Aged between 18 and 70 years Completion of (adjuvant) chemotherapy with curative intention and completion of surgical treatment or radiotherapy		Maxima Medical Center Veldhoven/ Eindhoven, Catharina Hospital Eindhoven, Elckerlieck Hospital Helmond, Sint Anna Hospital, Geldrop, VU University Medical Center Amsterdam
2. Exercise during chemotherapy	360	Histological confirmed primary breast of primary colon cancer who are scheduled to undergo adjuvant chemotherapy		Amstelland Hospital, Antoni van Leeuwenhoek Hospital, Bovenij Hospital, Flevohospital, Medical Center Alkmaar, Onze Lieve Vrouwe Gasthuis, Rode Kruis Hospital Beverwijk, Sint Lucas Andreas Hospital, Spaarne Hospital Hoofddorp, VU University Medical Center Amsterdam, Waterland Hospital, Zaans Medical Center
3. Exercise after SCT	120	Haematological malignancies undergoing high dose chemotherapy and autologous SCT Multiple myeloma in first line; Hodgkin's lymphoma or non-Hodgkin's lymphoma in first relapse Aged between 18 and 65 years Sufficiently recovered from the SCT and having peripheral blood recovery	Multiple myeloma undergoing a tandem autologous–allogeneic SCT Extensive osteolytic lesions with risk of fracture Severe infections	Academic Medical Centre Amsterdam, Antoni van Leeuwenhoek Hospital Amsterdam, University Medical Center Utrecht, Antonius Hospital Nieuwegein, Haga Hospital The Hague
4. Exercise during childhood cancer	100	Aged 8–18 years at the time of intervention Diagnosed with any type of childhood malignancy Treated with chemo- and or radiotherapy No longer than 12 months off treatment	Bone marrow transplantation Growth hormone treatment	Centre for Paediatric Oncology and Haematology of VU University Medical Center, Wilhelmina Children's Hospital University Medical Centre Utrecht, Emma Children's Hospital Academic Medical Center Amsterdam

SCT Stem cell transplantation

[a] All four studies exclude patients who are wheelchair dependent or not able to perform basic activities like walking or cycling, patients with contraindications for physical activity or exercise (i.e. serious orthopaedic conditions that would hamper functional recovery, serious cardiovascular or cardiopulmonary risks), patients with serious psychiatric or cognitive problems or severe emotional instability, patients suffering from malnutrition (evidenced by an unintended weight loss of more than 5% per month or more than 10% unintended weight loss during the previous 6 months), patients not being familiar with the Dutch language, patients who are unable to follow exercise instructions and patients participating in concurrent studies or rehabilitation programmes containing physical activity or exercise

verbally and via folders, about physical activity and provision of specific advice about the desired intensity of activity based on the Borg scale of rating perceived exertion.

In the studies evaluating the effectiveness of exercise interventions after and during chemotherapy, a second intervention arm is included consisting of low-to-moderate intensity exercise. Detailed descriptions of the interventions are presented elsewhere [25–28].

Assessments and Outcome Measures

All four A-CaRe trials use similar outcome measures, which are carefully chosen based on the International Classification of Functioning, Disability and Health (ICF) of the World Health Organization [32]. The ICF provides a useful framework for classifying the components of health and consequences of a disease. According to the ICF, the

consequences of a disease, in this case cancer (i.e. the type of cancer and its treatment), may concern body functions and structures, as well as the performance of activities and participation in life situations. Health states and the development of disability are modified by contextual factors including personal factors, such as sociodemographic data, and environmental factors, such as societal attitudes and social support [32]. Furthermore, cancer and its associated impairments, activity limitations and participation restrictions may have consequences for HRQoL (Fig. 2). In the ICF classification, the letters b, s, d and e refer to the following components of the classification: body functions, body structures, activities and participation and environmental factors. The hierarchical code system of the ICF consists of the abbreviation of the component and the chapter number (e.g. *b4 Functions of the cardiovascular*, *haematological*, *immunological* and *respiratory systems*), followed by the second level (e.g. *b455 Exercise tolerance functions*), the third level (e.g. *b4551 Aerobic capacity*) and possibly a fourth level. The use of a lower-level (more detailed level) category automatically implies that the higher-level category is also applicable.

In oncology rehabilitation, the ICF framework is suggested to be useful for selection of outcome measures [33]. In A-CaRe Clinical Research, the outcome measures are carefully selected to assess body functions as well as activities and participation. Table 3 presents an overview of the outcome measures and instrumentation that will be used in A-CaRe Clinical Research, classified according to the ICF. Primary outcome measures are cardiorespiratory fitness, muscle strength and fatigue. Secondary outcome measures include body composition, health-related quality of life, physical activity, mood and sleep disturbances, participation and autonomy, return to work and adverse events.

All outcome measures are assessed at baseline, prior to randomization (T0), at completion of the intervention (T1) and at follow-up (T2). Follow-up measurements will be performed 12 months after completion of the intervention. In the RCT evaluating exercise during chemotherapy, T2 measurements take place 6 months after completion of the intervention.

Primary Outcome Measures

Cardiorespiratory Fitness Cardiorespiratory fitness is measured during a maximal exercise test on an electronically braked cycle ergometer according to a ramp protocol [34], in which the resistance gradually increases every 6 s aiming to achieve the maximum within 8 to 12 min. For children and adolescents, the Godfrey protocol is used [35]. In this protocol, patients will begin pedalling at 0 W for 1 min, and the workload increases by 10, 15 or 20 W each minute depending on the patients' height and clinical status [35]. All patients are instructed to cycle with a pedal frequency between 70 and 80 rpm and are encouraged to continue exercising until exhaustion, or inability to maintain the pedal frequency of 70 rpm. Expired gases are collected and analysed breath by breath for O_2, CO_2 and volume. The average values of the last 30 s of exercise are used as measures for peak oxygen uptake (peakVO_2, in litres per minute), peak power output (peakW, in watt) and peak heart rate (HR). Ventilatory threshold is determined by using the oxygen equivalent method [36]. HR and respiratory exchange ratio are used as objective criteria for peak exercise.

In the RCT evaluating exercise during chemotherapy, peakVO_2 cannot be determined directly, due to logistic reasons. Therefore, an estimation of peakVO_2 is made based on the steep ramp test using a linear regression equation [30]. This has been shown to be a reliable (ICC=0.996) and valid method to estimate cardiorespiratory fitness in cancer patients [30]. In the other three A-CaRe trials, the steep ramp test is performed for adjustments of training intensities.

Muscle Strength Upper extremity muscle strength of adults is measured using a JAMAR grip strength dynamometer. Handgrip can be used to characterize general upper extremity muscle strength [37–39] and can increase after general upper extremity resistance training including exercises that did not specifically involve handgrip strength [40].

Lower extremity muscle strength of adults is tested by the functional 30-s chair stand test. This test is a valid and reliable measure of lower extremity strength in adults [41]. Patients are asked to stand upright from a chair with the arms folded across the chest, then to sit down again and repeat the action over a 30-s period. The number of times that the patient rises to a full stand from the seated position within 30 s is recorded [42–44].

For children and adolescents, upper and lower extremity muscle strength is assessed using a handheld dynamometer. Upper extremity muscles include grip, shoulder abductor and wrist extensor strength. In the lower extremity, muscle strength of the hip flexors and the knee and dorsal foot extensors is measured. Three consecutive measurements are performed using the 'break method', in which the examiner gradually overcomes the muscle force and stops at the moment the extremity gives way [45]. The highest value will be registered.

Fatigue In adults, fatigue symptoms are assessed with the Multidimensional Fatigue Inventory (MFI) [46]. The MFI contains 20 items, organized into five scales: general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue. The MFI subscales have good internal consistency (average Cronbach's alpha=0.84) [47].

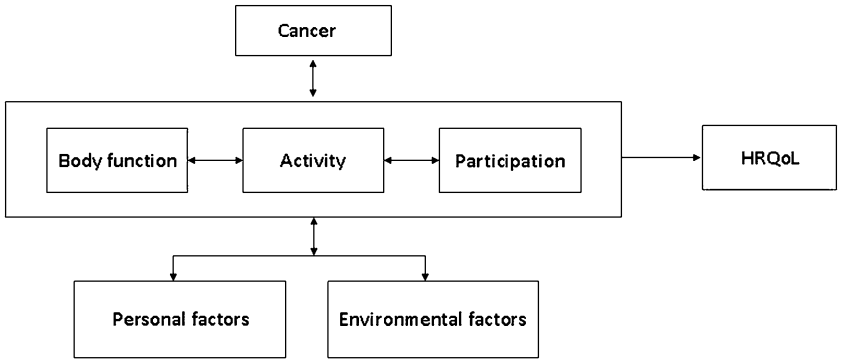

Fig. 2 The International Classification of Functioning, Disability and Health (ICF) model

In addition, adults' perception and appraisal of experienced fatigue are assessed with the Fatigue Quality List (FQL) [48]. The FQL consists of 25 adjectives describing the fatigue experience, organized into four subscales: frustrating, exhausting, pleasant and frightening.

Secondary Outcome Measures

Fatigue in Children In children, fatigue is assessed by the 18-item Paediatric Quality of Life Inventory (PedsQL) Multidimensional Fatigue Scale Acute Version, which is designed to measure both the child's and parents' perception of fatigue in paediatric patients [49]. It consists of three subscales: general fatigue (six items), sleep rest fatigue (six items) and cognitive fatigue. Both parent and child reports were shown to be valid and reliable in childhood cancer [49].

Mood Disturbances In adults, mood disturbances are assessed with the 14-item Hospital Anxiety and Depression Scale (HADS) [50, 51]. It yields a total score and separate scale scores for anxiety and depression. Numerous studies have applied the HADS to assess distress among cancer patients [52–54]. Furthermore, the questionnaire has been validated for use in the Dutch population [55].

The Children's Depression Inventory is used to assess symptoms of depression in children and adolescents with cancer. Overall, this questionnaire has good internal consistency and test–retest reliability and a positive correlation with clinicians' independent global depression ratings [56].

Sleep Disturbances Sleep disturbances are assessed with the Pittsburgh Sleep Quality Index (PSQI), an 18-item, self-rated questionnaire assessing the quality of sleep and sleep disturbances over a month [57]. A total score is derived as well as seven subscales that include subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction. Scores≥5 on the PSQI total scale, computed as the sum of the seven subscales are associated with clinically significant sleep disturbances [57].

Health-Related Quality of Life In adults, HRQoL is assessed with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), a questionnaire specifically developed to asses HRQoL in cancer patients [58]. It consists of 30 items, organized into five functional scales (physical, role, emotional, cognitive, social), three symptom scales (pain, fatigue and emesis) and an overall quality of life scale. Additional single items address other symptoms commonly experienced by cancer patients (e.g. insomnia, diarrhoea, constipation etc.). Validity and reliability of the questionnaire have been established [58].

HRQoL in children and adolescents with cancer is assessed by child self-report and parent-proxy report using the PedsQL 4.0 Generic Core Scale and the PedsQL 3.0 Cancer module. The PedsQL 4.0 Generic Core Scale is a 23-item questionnaire encompassing physical, emotional, social and school functioning domains. The PedsQL 3.0 Cancer module is a 27-item multidimensional cancer-specific questionnaire that encompasses eight scales: pain and hurt, nausea, procedural anxiety, treatment anxiety, worry, cognitive problems, perceived physical appearance and communication. Validity and reliability of both child and parent reports of the PedsQL Generic Core Scale and the Cancer Module has been shown [49, 59].

Self-Perception and Behavioural Problems in Children and Adolescents The Dutch version of the Self-Perception profile for children (CBSK) and adolescents (CBSA) is used to assess self-perception of scholastic competence, social acceptance, physical appearance, behavioural conduct, global self-worth and close friendships. The questionnaire has good reliability and validity when used in children 8 years and older [60, 61].

Internalizing and externalizing behavioural problems are assessed using the Dutch translated and validated

Table 3 The outcome measures and instruments used in the A-CaRe trials, classified according to the ICF

International Classification of Functioning, Disability and Health					
Second level		Third level		Adults	Children
Body functions					
Chapter 1	Mental functions				
b122	Global psychosocial functions				CBCL, YRS
b126	Temperament and personality functions				CBCL, YRS, CBSA/CBSK (behavioural conduct)
b130	Energy drive and functions			MFI, FQL	PedsQL Multidimensional Fatigue Scale Acute version
b134	Sleep functions			PSQI	
b152	Emotional functions			HADS	CDI
b280	Sensations of pain			EORTC QLQ-C30 symptom scale	
Chapter 4	Functions of the cardiovascular, haematological, immunological and respiratory systems				
b410–b429	Cardiovascular system functions			Heart rate	Heart rate
b440–b449	Respiratory system functions			Respiratory rate	Respiratory rate
b455	Exercise tolerance functions				
		b4551	Aerobic capacity	$PeakVO_2$	$PeakVO_2$
		b4552	Fatigability	MFI	
Chapter 5	Functions related to the digestive, metabolic and respiratory systems				
b530	Weight maintenance			BMI, skinfolds, hip and waist circumference, DEXA scan	BMI, DEXA scan
Chapter 7	Neuromusculoskeletal and movement-related functions				
b730	Muscle power function				
		b7304	Power of muscles of all limbs	Upper extremity: handgrip strength Lower extremity: 30 s chair stand test	Handheld dynamometer for upper and lower extremity
Activities and participation					
Chapter 4	Mobility				
d410	Changing basic body position				
		d4103	Sitting	30-s chair stand test	
		d4104	Standing	30-s chair stand test	
d450	Walking			PASE and accelerometer	Accelerometer
d460	Moving around in different locations			IPA (mobility and leisure)	
		d4600	Moving around within the home	IPA (mobility and leisure)	
		d4601	Moving around within buildings other than home	IPA (mobility and leisure)	
		d4602	Moving around outside the home and other buildings	IPA (mobility and leisure)	
d470	Using transportation	d4700	Using human-powered vehicles	PASE	
Chapter 5	Self-care				
d510	Washing oneself			IPA (autonomy in self-care)	
d530	Toileting			IPA (autonomy in self-care)	
d540	Dressing			IPA (autonomy in self-care)	
d550	Eating			IPA (autonomy in self-care)	
d560	Drinking			IPA (autonomy in self-care)	

Table 3 (continued)

International Classification of Functioning, Disability and Health					
Second level		Third level		Adults	Children
d570	Looking after one's health			IPA (autonomy in self-care)	
Chapter 6	Domestic life				
d620	Acquisition of goods and services				
		d6200	Shopping	IPA (family role)	
d640	Doing housework			PASE, IPA (family role)	
		d6402	Cleaning living area	IPA (family role)	
d650	Caring for household objects			IPA (family role)	
Chapter 7	Interpersonal interactions and relationships				
d750	Informal social relationships			IPA (social relations)	CBSA/CBSK (close friendships)
		d7502	Informal relationships with co-inhabitants	IPA (social relations)	
d760	Family relationships			IPA (social relations)	
d770					
		d7702	Sexual relationships	IPA (social relations)	
Chapter 8	Major life areas				
d810–d839	Education			Level of education	Level of education, return to school
					CBSA/CBSK (scholastic competence)
d815	Preschool education			Level of education	Level of education, return to school
d820	School education			Level of education	Level of education, return to school
d825	Vocational training			Level of education	Level of education, return to school
d830	Higher education			Level of education	Level of education, return to school
d840–d959	Work and Employment			Type of employment, return to work	
d850	Remunerative employment			Type of employment, return to work	
		d850	Self-employment	Type of employment, return to work	
		d8501	Part-time employment		
		d8502	Full-time employment	Type of employment, return to work	
d855	Non-remunerative employment			Type of employment, return to work	
d870	Economic self-sufficiency			IPA (family role)	IPA (family role)
d880	Engagement in play				Accelerometer
Chapter 9	Community, social and civic life				
d920	Recreation and leisure			IPA (mobility and leisure)	IPA (mobility and leisure)
		d9200	Play		Accelerometer
		d9201	Sports	PASE and accelerometer	Accelerometer

BMI body mass index, *CBCL* Child Behaviour Checklist, *CBSA* self-perception profile for adolescents, *CBSK* self-perception profile for children, *CDI* Child's Depression Inventory, *DEXA* dual energy X-ray, *EORTC QLQ-C30* European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire C30, *FQL* Fatigue Quality list, *HADS* Hospital Anxiety and Depression Scale, *IPA* Impact on Participation and Autonomy, *MFI* Multidimensional Fatigue Inventory, *PSQI* Pittsburgh Sleep Quality Index, VO_2 oxygen uptake

Child Behaviour Checklist (CBCL) for children younger than 11 years. The CBCL is a valid and reliable instrument to assess the parents' evaluation of internalizing and externalizing behaviour problems of children [62]. For children aged 11 to 18 years old, the Youth Self Report is used.

Functioning in Daily Life The Impact on Participation and Autonomy (IPA) Questionnaire is used to assess functioning in daily life of adults [63]. The IPA consists of 32 items assessing perceived level of participation and autonomy, organized into five domains: autonomy in the home, family role, autonomy outside of the home, social relations and work and education. An additional nine items assess perceived problems with participation and autonomy. Internal consistency of the five domain scores range from 0.81 to 0.91.

Physical Activity Objective levels of physical activity are assessed using an accelerometer, a small and lightweight device, which detects accelerations. Patients wear the accelerometer on the right hip attached to a belt for 4–7 days, including at least one weekend day. Although accelerometers may underestimate some activities, such as cycling and water activities, it is recognised as a reasonably valid tool to objectively assess physical activity in adults [64], as well as in children [65–67]. Accelerations are converted into activity counts per minute, indicating the level of physical activity.

Self-reported physical activity of adults is assessed using the Physical Activity Scale for the Elderly (PASE). The PASE is a brief, self-administered 7-day recall questionnaire, which consists of questions on leisure time, household and work-related physical activities [68]. The frequency of activities is recorded as never, seldom (1 to 2 days/week), sometimes (3 to 4 days/week) or often (5–7 days/week). The duration of activities is categorized as less than 1 h, between 1 and 2 h, between 2 and 4 h or more than 4 h. Paid or unpaid work, except for work that involves mostly sitting activities such as office work, is categorized as less than 1 h, between 1 and 4 h, between 5 and 8 h or more than 8 h [69]. The total activity score is computed by multiplying the amount of time spent on each activity (in hours per week) by the empirically derived item weights and summing over all activities [68]. In healthy adults, the PASE has shown to have high test–retest reliability (r=0.84) [68] and reasonable validity as compared with the doubly labelled water method (r=0.58) [70]. Results from our institution showed that the PASE had good to excellent test-retest reliability in cancer patients and good content validity [71].

Body Composition Body height and body weight are assessed in all patients, and BMI is calculated. In addition, fat mass, muscle mass and bone mineral density will be assessed by whole body dual energy X-ray scans in adults, children and adolescents, except for participants from the exercise intervention during chemotherapy, due to logistic reasons. In adults, also waist and hip circumferences and thickness of four skinfolds (biceps, triceps, suprailiacal, subscapular) are assessed.

Return to Work or School The following indicators of return to work (RTW) or school (RTS) are measured using self-reported calendars: time to partial and to full RTW or RTS expressed in number of calendar days between the end of treatment and the first day at work, time to full RTW or RTS corrected for partial RTW or RTS and partial and full RTW or RTS rate at T0, T1 and T2.

Covariates

Sociodemographic and Clinical Data Sociodemographic data, including age, (parental) education, marital status, living situation, work (or school) status, medication use and lifestyle variables (e.g. smoking, physical activity prior to diagnosis), are collected at baseline.

Clinical information is collected from the medical records and includes date of diagnosis, stage and subtype of disease, treatment history, type and dose of chemotherapy and/or radiotherapy and adverse events during treatment. During the follow-up period, data on disease status (response to treatment, progression or relapse) and data on any additional treatment are collected.

Moderating Variables At baseline, a series of questions is asked to assess potential moderating variables including pre-illness lifestyle (frequency, nature and intensity of physical activity and exercise behaviour, or avoidance thereof), current attitudes towards and beliefs about exercise in general and exercise during or after treatment. Information about behavioural, normative and control beliefs about exercise, attitude towards exercise, subjective norm, perceived behavioural control and intention is collected using standardized questions as described by Courneya et al. [72, 73]. These questions have previously been used to evaluate exercise programmes in cancer patients and survivors and are based on established health behaviour theories, in particularly the Theory of Planned Behaviour [74].

Adherence Compliance with the interventions is assessed by self-report, and attendance and exercise logs filled in by physical therapists and psychologist (e.g. observed attendance at and compliance with the exercise). Non-responders and dropouts receive a short questionnaire to assess the reason for non-participation or dropping out of the study.

Satisfaction with Intervention After completion of the intervention programmes, patients are asked to complete a brief questionnaire addressing the perceived efficacy of and satisfaction with the programme, whether they would suggest any changes to the programme and if they would recommend it to other patients undergoing similar treatments.

Adverse Effects Adverse effects of the rehabilitation programmes in adult patients are actively monitored during the study with a special emphasis on increased fatigue, reported by the patients, physiotherapists, sports physicians or trainers and checked in the medical records. In addition, in patients from the RCTs that evaluate training after chemotherapy and after stem cell transplantation, neurotoxicity is evaluated using the Chemotherapy-Induced Peripheral Neuropathy (CIPN20) questionnaire [75]. This is an EORTC quality of life questionnaire that is specifically developed to assess chemotherapy-induced peripheral neuropathy.

Costs from a Societal Perspective

Besides the costs of the exercise programmes, data on health care costs, patient and family costs and costs of production losses are collected using monthly cost diaries measured on a three-monthly basis during the entire follow-up period. Health care costs include the costs of oncological care, general practice care and physiotherapy, additional visits to other health care providers, prescription of medication, professional home care and hospitalization. Patient and family costs include out-of-pocket expenses such as travel expenses and costs for paid and unpaid help. Costs related to production losses include work absenteeism for patients (or parents) with paid jobs and days of inactivity for patients (or parents) without a paid job.

Utilities are measured using the EuroQol (EQ5D) [76]. The EQ5D is a health-related quality of life measure that provides a single index of an individual's quality of life. It consists of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety and depression. Each dimension is rated as 'no problem', 'some problem' or 'extreme problem', resulting in 243 possible health states [76]. Dutch tariffs will be used to value these health states [77].

Statistical Analyses

Data will be analysed on an intention-to-treat basis, in which all patients will be included in the group they were allocated to by randomization. In addition, a per-protocol analysis will be performed in which we only include participants who completed the intervention they were allocated to according to the protocol. Completing the intervention is defined as having attained 75% of all training sessions.

Multi-level longitudinal regression analysis will be conducted to assess between-group differences in each outcome measure. The follow-up value will be defined as the dependent variable and the following levels will be used: (1) time of follow-up measurement (values corresponding with performance at T1 and T2), (2) training centre and (3) individual. Regression coefficients indicate differences between intervention and control groups. Regression models will be adjusted for the baseline values of the respective outcome measures. Missing values will be avoided as much as possible by asking participants to comply to the post-test and follow-up measurement even after they drop out from the exercise programme. Missing values will be accounted for in the mixed linear regression modelling.

Costs are valued using the guidelines published in the updated handbook for economic evaluation in The Netherlands, issued by the Dutch Health Care Insurance Board [78]. Both incremental cost-effectiveness and cost–utility analyses are performed. The cost-effectiveness ratio is calculated by dividing the difference between the mean total costs of the exercise and control groups by the difference in mean effects of the group(s) [79]. The primary clinical effect measures of the trials will be included in the cost-effectiveness analyses. The cost–utility ratio expresses the additional costs of the intervention compared with the control group per quality adjusted life years. Cost-effectiveness and cost–utilities ratios are estimated using bootstrapping techniques and uncertainty of these ratios graphically presented on cost-effectiveness and cost–utility planes, and acceptability curves [79, 80]. Sensitivity analyses on the most important cost drivers are performed in order to assess the robustness of results.

Discussion

This paper presents the design and methods of four randomized controlled trials on exercise-based rehabilitation programmes included in the A-CaRe Clinical Research programme. These studies are designed to evaluate the effectiveness and cost-effectiveness of exercise-based rehabilitation programmes in different cancer patient and survivor groups. The outcome measures of the studies are carefully chosen based on the ICF, and the instrumentation is standardized, valid and reliable. It is hypothesized that exercise-based rehabilitation programmes are more effective at improving cardiorespiratory fitness and muscle strength, and thereby reducing fatigue, and more cost-effective compared with usual care or a waiting list control group. In addition, we compare the results of high-intensity training to low-to-moderate intensity training.

Unlike cardiovascular diseases or other chronic conditions, exercise-based rehabilitation programmes are currently not part of standard health care for cancer patients and survivors in The Netherlands. Before being able to implement cancer rehabilitation programmes on a large scale, the efficacy of such programmes need to be established. This is the main aim of the A-CaRe programme. In addition to the evaluation of the effectiveness and cost-effectiveness of the exercise interventions, we need to gain insight in how (mediators), for whom

and under what circumstances (moderators) these interventions are effective. Insight in mediators and moderators of exercise interventions is essential to be able to tailor cancer rehabilitation programmes to the needs, preferences and characteristics of individual cancer patients. With the large database resulting from the four A-CaRe trials, we will be able to explore several mediators and moderators of exercise-based cancer rehabilitation programmes.

In conclusion, the four A-CaRe trials evaluate the effectiveness and the cost-effectiveness of various exercise-based rehabilitation programmes in cancer patients and survivors, in comparison with usual care or no treatment.

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