Methodological considerations when monitoring and promoting physical activity in cancer populations

Towards translation of evidence into broader application and impact

Benedikte Western

UiA University of Agder

Doctoral Dissertations at the University of Agder 472

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Preface

Booth, Colomb, and Williams write: "… no matter how carefully you plan, research follows a crooked path, taking unexpected turns, sometimes up blind alleys, even looping back on itself" (Booth, Colomb, & Williams, 2008). This is a fairly accurate description of how this thesis came together over the past four years. When starting as a PhD candidate in 2020, I was originally part of a large, nationwide, hospital-based intervention study that was using e-health to promote physical activity and lifestyle change among Norwegian gynaecological cancer survivors. However, after nearly 12 months of Covid-19 out-brakes and lockdowns, despite tireless work of nurses, doctors, and research staff, we had to come to terms with the fact that we were not going to reach the required number of participants in time to include the data in the present thesis. That meant we had to take a new approach to the aim and content of this thesis. As a result, I was truly introduced to the field of exercise oncology and the large community within, with researchers dedicated to improving the lives of cancer survivors around the world through a mean that is, in some form or another, accessible, controllable, and adaptable to anyone: physical activity and exercise. Through this community I got the opportunity to work with data from several different studies and I got to learn from some of the greatest names within this field (including my great team of supervisors, without whom none of this would have been possible).

Still, I found myself inspired by the pragmatic study we were working on even during a pandemic. I wanted to contribute with evidence that could further inform such trials in the future. As a result, the focus of this thesis became the methodology of studies measuring and promoting physical activity and exercise in the cancer population.

Several individuals have been imperative during the period of writing this thesis. As mentioned, this thesis would not have been possible without my supervisors *Sveinung Berntsen*, *Ingvild Vistad*, and *Ingrid Demmelmaier*. By having immense knowledge within your respective fields, you have contributed with valuable insights and guidance, and helped me come in contact with different research communities, also outside of Norway. This has inspired me and help me to view my thesis from both a sport science, clinical, and behavioural change perspective, which, combined with my public health background, have given me a broader perspective of the research topics. Thank you for your supervision, support, and encouragement. Thank you for believing in me although some obstacles were faced along the way, and for grounding me when things felt overwhelming.

Secondly, I would like to thank my partner Tommy, and my family and friends for all your support and encouragement during this period. *Tommy*, you have been invaluable with your support, humour, and positive attitude. You have contributed with ideas, kept my blood sugar stable, and listened to my rants when I have needed to vent. Thank you, *pappa* for reading my many drafts and to *mamma* for being my biggest cheerleader. Thank you to my sister *Hedvig*, for always giving me your honest takes, and my brother *Joachim*, for our many

geeky discussions and for watching the cats when a vacation has been needed. I would like to thank *morfar* for teaching me about hard work and dedication, but also about enjoying life and seizing the day. I am so happy you were there to see me on this journey, but I really wish you could have been here today.

Furthermore, I want to thank you fellow phd students and colleagues who have made this time so memorable and fun. I have cherished our time together, from traveling to international conferences, to having a beer at the local bar, and to the daily chats over a cup of coffee. Without you and these moments, my time as a PhD student would have lacked an important dimension. Especially thank you to *Per Thomas*, *Synne*, *Lena*, and *Susanne*, who have played significant roles in my everyday life at the University.

I would also like to extend my gratitude to the LETSGO team *Anita, Jorid, Mette, Ingvild, and Sveinung.* Thank you for the experiences we have shared together during the past years. These moments and collaborations have contributed a lot to making my PhD journey enjoyable, both at and outside of work.

This journey has put me on a path I could never have imagined, resulting in me finding a passion in data science. This would not have been possible without the people around me. Especially thank you to *Sveinung* who have listened to all my ideas, encouraged me when I have wanted to try these ideas, and contributed with your insights throughout. Without this support I may not have stumbled upon this opportunity.

Thank you.

Benedikte Western

Kristiansand, February 2024

Summary

The prevalence of cancer is rising in accordance with the expanding global population of increasingly older individuals. Lifestyle factors and behaviours of modern-day life, such as inactivity and more sedentary time, are also associated with an increasing risk of cancer. Today, individuals diagnosed with cancer often live long lives after being treated or on long-term treatment. Yet, life beyond cancer can come with its own set of challenges, including the presence of health impairments emerging after cancer treatment. Physical activity and exercise have been associated with significant improvements in several of these health impairments. Thus, cancer survivors are generally recommended to engage in physical activities at moderate-to-vigorous intensity for 150 minutes or more each week, and to perform muscle strengthening exercises twice a week. However, few cancer survivors comply with these recommendations.

Despite the numerous benefits of physical activity, widespread implementation and accessibility of exercise programs and self-management support in the cancer care are lacking. One reason for this may be the limited proportion of research dedicated to conducting pragmatic research directly relevant for real-world settings. Most research have been carried out in ideal, well-resourced settings that may not be applicable to practice. Consequently, cancer survivors are deprived of potential benefits while the burden on the health care system is increasing. As the population of cancer survivors continues to expand, the promotion of long-term health should be a central goal of the cancer survivorship care. The cancer care should provide a follow-up regime that enables and equips cancer survivors to self-manage their health including performance of behaviours such as physical activity, that can positively affect their health and wellbeing long-term. This will require translation of current evidence and knowledge into broader application and impact, which can further inform pragmatic trials and implementation. The overarching aim of the present thesis was to explore unaddressed areas in the literature and close research gaps related to methodological components of studies measuring and promoting physical activity and exercise in cancer populations.

Accurate measures of time spent in physical activity intensities is crucial in trials investigating effects of, or changes in, physical activity levels. Wearable devices, often referred to as objective monitoring, is generally considered more accurate compared to self-report methods. However, the applied monitoring protocol can

impact the reliability of the physical activity data and may have implications for study participation and dropout. Currently, there is no consensus on how physical activity data should be collected through wearable devices in cancer populations. Thus, there is great heterogeneity in methods applied across studies, which limits the comparability of results. The first objective was to obtain the minimum monitoring period required for reliable estimates of device-based physical activity levels among cancer survivors. A six-days continuous monitoring protocol was applied in a pooled sample of breast, colorectal, and prostate cancer survivors. Intra-class correlation coefficients and the Spearman Brown prophecy formula were used to determine the minimum reliable monitoring period from these measures. Overall, two monitoring days for light intensity, and three monitoring days for moderate and moderate-to-vigorous intensity resulted in reliable estimates. The intra-individual variation in vigorous intensity physical activity was substantial and reliable estimates were not obtained across the six days.

Randomized controlled exercise trials conducted in cancer populations are contributing to the evidence base of exercise effects. However, the sample of these trials are often prone to selection bias and may not be representative of all cancer survivors. Furthermore, trials typically experience varying degrees of dropout, which may potentially bias the samples further. Although this has great implication for external validity and may possibly inform assessments of feasibility, dropouts are seldomly assessed. The second objective was to assess participant and intervention characteristics associated with dropout from exercise interventions. Thirty-four randomized controlled exercise trials including 2467 cancer survivors were harmonized. Dropout was identified based on missing all data post-intervention and associations with dropout were explored using a conditional inference tree algorithm. In total, 9.6% of the sample dropped out, however, the dropout rates varied significantly based on the significant associations that divided the sample into five subgroups. The two subgroups exhibiting particularly high dropout rates compared to the other participants were cancer survivors with BMI >28.4 kg/m^2 who participated in resistance exercise interventions or unsupervised mixed exercise interventions (19.8% dropout), and the remaining cancer survivors with BMI >28.4 kg/m^2 who had low-medium education (13.5% dropout). Among participants with BMI ≤28.4 kg/m^2, dropout

was significantly higher among participants performing exercise post-treatment as opposed to during treatment.

Little is known about the specific aspects of self-management that may contribute to improved physical activity levels after self-management support interventions. Thus, there is a need for exploring self-management skills related to physical activity behaviours, and vulnerable and less studied subgroups should be targeted. The third objective was to assess self-management skills associated with physical activity participation among gynaecological cancer survivors. The association between different dimensions of self-management representing various self-management skills, and physical activity participation was assessed among 1433 survivors of endometrial, ovarian, and cervical cancer. The sample was recruited from the Netherlands, Norway, and Denmark, and the Health Education Impact Questionnaire was used to measure self-management dimensions, including physical activity participation. Linear regressions adjusted for participant characteristics were applied to investigate the strength of the associations across the self-management skills and physical activity participation. The strongest associations were observed for Positive and Active Engagement in Life and Self-Monitoring and Insight. Thus, the more active participants appeared to be more actively engaged in their life, planned and prioritized activities and hobbies they found enjoyable, and were motivated to improve their life-circumstances. They also possessed self-monitoring skills, an ability to self-manage their condition by taking appropriate actions when symptoms worsened, had reasonable expectations to themselves, and had insight into their health issues and factors affecting these.

In the present thesis, reliable physical activity estimates were found for a shorter, more applicable, less resource demanding, and potentially less burdensome monitoring period. Significantly higher dropout, thus less complete data, was found in some subgroups across different exercise trials, possibly compromising external validity and generalizability of trial results. Certain self-management skills appeared more strongly associated with physical activity participation among gynaecological cancer survivors. While further research is required to establish the behavioural impact of these skills, the results may inform the design of future interventions.

Sammendrag

Forekomsten av kreft stiger parallelt med den globale befolkningsveksten og økt levealder. Livsstilsfaktorer og atferder slik som inaktivitet og stillesitting er assosiert med høyere risiko for å utvikle kreftsykdommer. Selv om personer som diagnostiseres med kreft i dag ofte lever lange liv etter behandling eller på langtidsbehandling, kan flere utfordringer oppstå i ettertid slik som svekket helsestatus og senskader. Fysisk aktivitet og trening er assosiert med signifikante forbedringer i flere av disse helseutfordringene. Derfor anbefales kreftoverlevere generelt å være i fysisk aktivitet med moderate til høy intensitet 150 minutter eller mer hver uke, samt utføre muskelstyrkende aktiviteter to ganger i uka. Til tross for dette er det få kreftoverlevere som oppfyller disse anbefalingene.

Selv om mange helseforedeler har blitt observert i sammenheng med fysisk aktivitet etter en kreftdiagnose, finnes det enda ingen utbredt implementering av fysisk aktivitet og hjelp til selvledelse i kreftomsorgen. En grunn til dette kan være at lite forskning har fokusert på pragmatiske studier i praksisnære settinger. Forskningen har hovedsakelig blitt utført i ideelle setting med mye ressurser, som ikke nødvendigvis representere virkelighetskontekster. Som en konsekvens går mange kreftoverlevere glipp av flere potensielle helsefordeler samtidig som belastningen på helsevesenet øker. Da andelen kreftoverlevere fortsetter å øke burde langsiktig helse være et sentralt mål i kreftoppfølgingen. Kreftoppfølgingen bør inkludere et oppfølgingsregime som gjøre kreftoverlevere i stand til å håndtere sin egen helse, inkludert å utføre helsefremmende aktiviteter. Dette vil kreve forskning informert av nåværende evidens, men med bredere anvendelse og påvirkning, videre pragmatiske studier og implementering. Det overordnede målet i denne avhandlingen var å lukke kunnskapshull relatert til metodologiske komponenter i studier som måler og fremmer fysisk aktivitet i kreftpopulasjoner.

Presise målinger av fysisk aktivitet er viktig i studier som undersøker effekten av, eller endringer i, fysisk aktivitetsnivå. Aktivitetsmålere blir ofte omtalt som objektive målemetoder og er ansett som mer nøyaktige sammenlignet med selvrapportering. Likevel kan protokollen man anvender for hvordan aktivitetsmålerne brukes, påvirke reliabiliteten til aktivitetsdataene, studiedeltakelse og frafall. For øyeblikket er det ingen konsensus rundt hvordan aktivitetsmålere burde brukes, altså hvilke protokoller som burde følges. Det er derfor store forskjeller mellom metodene som anvendes i ulike studier, noe som

begrenser sammenligning av resultater på tvers av studier. Det første målet i denne avhandlingen var å finne den korteste måleperioden for reliable estimater av fysisk aktivitet blant kreftoverlevere ved bruk av en aktivitetsmåler. En seksdagers kontinuerlig måleperiode ble brukt i et utvalg av personer med bryst-, kolorektal-, og prostatakreft. Intraklassekorrelasjon og Spearman Brown prophecy formelen ble brukt til å finne den korteste reliable måleperioden. Samlet sett var to dager med måling tilstrekkelig for reliable estimater av fysisk aktivitet med lett intensitet, og tre dager tilstrekkelig for reliable estimater av moderat og moderat-til-høy intensitet. Den intraindividuelle variasjonen i fysisk aktivitet med høy intensitet var stor, og reliable estimater ble ikke funnet for høy intensitet i løpet av måleperioden.

Randomiserte kontrollerte treningsintervensjoner gjennomført i kreftpopulasjoner har i stor grad bidratt til evidensen rundt effektene av fysisk aktivitet og trening. Utvalgene i disse studiene er dog ofte preget av seleksjonsbias og er ikke nødvendigvis representative. I tillegg opplever mange av studiene frafall i løpet av studieperioden, noe som potensielt kan føre til enda større bias i det gjenværende utvalget. Selv om dette kan ha store implikasjoner for studiens eksterne validitet, og kan potensielt si noe om studiens gjennomførbarhet, er det sjelden at dette adresseres. Det andre målet i denne avhandlingen var å studere hvilke kreftoverlevere som i større grad falt fra studier med en treningsintervensjon. Trettifire randomiserte kontrollerte studier med totalt 2467 deltakere ble harmoniserte. Frafall ble definert for deltakere som ikke gjennomførte målinger etter intervensjonen og dermed manglet all oppfølgingsdata. Karakteristikk signifikant assosiert med studiefrafall ble analysert med et beslutningstre. Total manglet 9.6% av deltakerne oppfølgingsdata, men denne andelen varierte signifikant mellom fem definerte subgrupper identifisert via fire signifikante assosiasjoner. De to subgruppene med størst frafall var kreftoverlevere med en kroppsmasseindeks >28.4 kg/m^2 som enten deltok i styrketreningsintervensjoner (19.8% frafall), eller som hadde lav-til-middels utdanning (13.5% frafall). Hos deltakerne med en kroppsmasseindeks ≤28.4 kg/m^2 var frafallet større hos kreftoverlevere som deltok i treningsintervensjoner etter kreftbehandling, sammenlignet med de som trente under behandling.

Det er lite forskning på hvilke aspekter av selvledelse som kan føre til økt deltakelse i fysisk aktivitet. Det er derfor et behov for å utforske hvilke

egenskaper relatert til selvledelse som kan føre til mer fysisk aktivitet, samt å fokusere på utsatte grupper. Det tredje målet i denne avhandlingen var å måle hvilke dimensjoner innen selvledelse som viste sterkest assosiasjon med fysisk aktivitet blant overlevere av gynekologisk kreft. Totalt 1433 kvinner tidligere behandlet for kreft i livmor, eggstokk, og livmorhals, fra Nederland, Norge og Danmark deltok. Et spørreskjema ble brukt for å registrere ulike dimensjoner innen selvledelse og fysisk aktivitet. En lineær regresjon justert for deltakerkarakteristikk ble anvendt for å vurdere signifikansen og styrken på assosiasjonene. To dimensjoner viste sterkest assosiasjon. Deltakere som rapporterte å være aktivt engasjert i livet sitt, som planla og prioritere foretrukne aktiviteter og hobbyer og som var motivert til å forbedre omstendighetene sine, rapporterte også mer deltakelse i fysisk aktivitet. Mer deltakelse i fysisk aktivitet ble også rapportert hos de som oppga en større evne til å selvmonitorere helsen sin, som tok nødvendige grep ved forverring i helsestatus, som hadde oppnåelige forventninger til seg selv, og som hadde innsikt i hvilke faktorer som forverret helsen deres.

I denne avhandlingen ble det funnet at reliable estimater av fysisk aktivitet kan oppnås med en kortere, mer anvendelig, mindre ressurskrevende, og potensielt mindre belastende måleperiode. Signifikant mer frafall fra treningsintervensjoner ble funnet blant visse subgrupper på tvers av ulike studier, noe som potensielt svekker ekstern validitet og generaliserbarhet av intervensjonseffekter. Gitte dimensjoner av selvledelse er sterkere assosiert med fysisk aktivitet blant overlevere av gynekologisk kreft. Disse resultatene kan informere design av fremtidige intervensjoner, mens videre forskning er nødvendig for å vurdere påvirkningen disse aspektene av selvledelse kan ha på endring i fysisk aktivitetsnivå.

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Western, B., Demmelmaier, I., Vistad, I., Hansen, B. H., Stenling, A., Henriksen, H. B., . . . Berntsen, S. (2023). How many days of continuous physical activity monitoring reliably represent time in different intensities in cancer survivors. PLoS One, 18(4), e0284881. doi:10.1371/journal.pone.0284881

Paper II

Western, B., Ivarsson, A., Vistad, I., Demmelmaier, I., Aaronson, N. K., Radcliffe, G., . . . Buffart, L. M. (2024). Dropout from exercise trials among cancer survivors - An individual patient data meta-analysis from the POLARIS study. Scandinavian journal of medicine & science in sports, 34(2), e14575. doi:https://doi.org/10.1111/sms.14575

Paper III

Western, B., de Rooij, B. H., Ezendam, N. P. M., Berntsen, S., Demmelmaier, I., Skorstad, M., … Vistad, I. Dimensions of self-management associated with physical activity participation among gynecological cancer survivors: results from the cross-sectional multi-national InCHARGE study.

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List of abbreviations

BMI	Body Mass Index
CART	Classification And Regression Tree
CI	Confidence Interval
CRC-NORDIET	the Norwegian Dietary Guidelines and Colorectal Cancer Survival
Ctree	Conditional inference tree
CV	Coefficient of variation
EPIS	Exploration, Preparation, Implementation, and Sustainment
FIGO	Federation Internationale de Gynecologie et d'Obstetrique
HeiQ	the Health education impact Questionnaire
ICC	Intra-class Correlation Coefficient
InCHARGE	the International Collaboration of Healthcare professionals and Researchers for Gynaecologic Cancer Survivors' Empowerment study
IQR	Interquartile Range
Kg	Kilogram
M^2	Meters squared
MET	Metabolic equivalents
MVPA	Moderate-to-Vigorous Physical Activity
PAL	Physical Activity Level
Phys-Can	the Physical Training and Cancer study
POLARIS	Predicting Optimal cancer Rehabilitation and Supportive care
RCT	Randomized Controlled Trial
SD	Standard Deviation

SWAM	SenseWear Armband Mini
USA	United States of America

1 Introduction

Humans have pursued knowledge for centuries, and scientific inquiry, with its ancient roots, has evolved into a formalized discipline with established methodologies and structures. Historically, you could risk your life when opposing the established “truths” in search for new knowledge. Today, research is central in many parts of society and progress in numerous fields is a result of scientific advances. Research is involved in informing policies and decision makers, developing new technologies, advancing health care, and is our hope in tackling climate change and solving the energy crisis. However, the knowledge and evidence we rely on depends on the quality of the research that supports it and the accuracy of its reporting [1].

The methodology of scientific research is multifaceted and encompasses a broad range of components scientists must decide on, critically appraise, and report clearly and accurately. This can include the research design, theoretical framework, selection of study sample, data collection procedures, data analyses, ethical principles, intervention design, and the reporting and replicability of findings. In other words, the methodology of scientific research refers to all the components that come together to generate reliable and valid scientific knowledge.

Based on the design, sample, applied methods, and chosen endpoints of a study, all research trials can be placed on a continuum ranging from explanatory trials to pragmatic trials [2]. Explanatory trials, often known as efficacy trials, play a crucial role in providing knowledge concerning the effects of precisely defined interventions, typically applied to select groups under optimal conditions in well-resources settings [2]. The objective of explanatory trials is to confirm a hypothesis regarding a causal relationship between the intervention and an outcome [2, 3]. Thus, the interventions are usually strictly enforced with close monitoring of adherence, often excluding poorly adherent participants at risk of diluting the intervention effects [4]. The gold standard for explanatory trials is randomized controlled trials (RCTs) testing an intervention in a highly controlled setting. These trials minimize the risk of bias and threats to the internal validity of the study, i.e., the extent to which the study is able to accurately measure the effect of the intervention, and is the most appropriate research design for establishing causal relationships between an exposure and an outcome [5]. However, the results of these interventions may lack external validity, i.e., the

extent to which the results can be generalized beyond the specific conditions, participants, and settings in which the research was conducted. Furthermore, the interventions may be impossible to replicate or apply in practice.

Pragmatic trials, often referred to as effectiveness trials, are designed and conducted to maximize applicability to usual care settings [2]. Thus, different considerations of the trial setting, study sample, choice of outcome, and length of follow-up are made when designing pragmatic versus explanatory trials. While the explanatory trial has rigor selection of participants with definite inclusion and exclusion criteria, the pragmatic trial has little selection of participants beyond the clinical indication of interest [2]. The interventions of pragmatic trials are often more flexible and the outcomes should be directly relevant to participants, health care practitioners, communities, and funders [2]. They are also designed to meet the needs of those making decisions, e.g., about treatment options in the setting in which the intervention will be implemented.

To provide evidence relevant for healthcare settings, interventions are often initially tested in small and short trials placed at the explanatory end of the continuum [2]. If benefits are observed in such trials, larger explanatory trials, ideally RCTs, are conducted to verify the effects. Subsequently, trials towards the pragmatic end of the continuum must be conducted to establish the applicability of the intervention and findings to real-world settings. If this progression is neglected, the interventions risk becoming a lost opportunity to influence clinical practice and healthcare delivery, depriving potential receivers of valuable benefits.

The global population of cancer survivors continues to grow, and many cancer survivors are expected to live long lives after their cancer diagnosis [6]. Thus, promoting long-term health should be a central goal of the cancer survivorship care, especially since cancer survivors will eventually lose the frequent medical monitoring and support provided during follow-up. Some survivors may experience vulnerability and loss of a “safety net”, realizing that their life or health may not return to normal, and must adapt to fundamental changes that have taken place [7]. If not addressed, these survivors risk living unnecessarily restricted lives, social isolation, and dependence on others. Thus, the cancer care should provide a follow-up regime that enables and equips cancer survivors to self-manage their health, including performance of behaviours (e.g., physical activity) that can positively affect their health and wellbeing long-term [8].

Physical activity facilitation aligns directly with two of the four points defined as the most ideal components of the cancer survivorship care [9]. These are i) prevention of recurrent or new (primary) cancer and other late-effects, and ii) interventions to improve cancer- and treatment-related late-effects [9].

Throughout the literature, results from explanatory trials have been presented as compelling evidence for implementing physical activity and exercise in the cancer care [8, 10]. However, the methodology of this research may not be appropriate to inform this objective. To bridge this gap, a preparation phase of translating evidence into research with broader application and impact may be necessary [11]. This could encompass establishing consensus on measurement tools and patient-reported outcomes suitable for implementation research, devising targets and strategies to achieve accessible tailored programs across populations and care sectors, determining what recipients should attain and how to support them, exploring how to make patients partners in their care, and studying the active involvement of recipients, deliverers, and stakeholders [8].

2 Background

2.1 Cancer

Cancer has become a global health burden and a leading cause of death, affecting people of all ages and from all countries [6]. Worldwide, an estimated 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred in 2020 [6]. Characterized by the uncontrolled growth and spread of abnormal cells, cancer can manifest as tumours that invade nearby tissues and metastasize to other parts of the body [12]. The location, form, and severity (malignancy) of cancer cells and tumours vary, leading to large differences in symptoms, progression rates, disease severity, suitable treatment options, and prognosis [12].

In 2020, female breast cancer surpassed lung cancer as the most diagnosed cancer type, constituting 11.7% of the global cancer incidence [6]. Following female breast cancer, lung (11.4%), colorectal (10.0%), prostate (7.3%), and stomach (5.6%) cancers are most frequently diagnosed. However, geographical variations exist in the incidence and mortality of different cancer types, influenced by factors such as age, sex, lifestyle, environment, and genetics [13]. Consequently, while cancer predominantly affect older individuals, the demographic diversity within the cancer population is substantial.

Large variations in attributed risk have been found across cancer types [14]. Inherited predispositions, environmental and behavioural factors, and random mutations arising during DNA replication can cause cancers to varying degrees [14]. However, only a small proportion of cancer cases are attributed to genetic defects, whereas a larger proportion of cancer cases are rooted in environmental and lifestyle factors [15]. Physical inactivity, diet, overweight and obesity, unprotected sex, smoking, and alcohol use are some of the environmental and behavioural factors associated with an increased risk of cancer [13]. The association between physical activity and cancer risk was first documented in the 1980s when it was observed that women who were former college athletes had significantly lower risk of gynaecological cancer and breast cancer compared to non-athletes [16]. Physical inactivity has since been identified as a risk factor for several types of cancer [17]. Laboratory and observational studies have shown that physical inactivity in conjunction with diet and obesity, may also impact cancer recurrence and overall survival [15, 18].

The global burden of cancer is expected to rise parallel to the growing and increasingly older population [6]. Nevertheless, age-standardized mortality rates have declined for many cancer types, although less pronounced in some parts of Asia, South Africa, and Latin America [19]. Declines in mortality are largely attributed to improved treatment options and implementation of effective cancer control measures (e.g., screening). Consequently, an increasing number of individuals are expected to survive cancer and live for several years after diagnosis, resulting in an expanding population of cancer survivors.

Currently, there is no consensus on the definition of a "cancer survivor" [20, 21]. Some researchers have referred to cancer survivors as individuals who have lived 5 years or more post-diagnosis [20]. However, the most widely used definition refers to cancer survivorship as a process that begins at the moment of diagnosis and persists through life [20]. In the current thesis, the term cancer survivor will be used in accordance with this definition, thus, the term "cancer survivor" will be used for any individual who has been diagnosed with cancer at any point in life and is still alive.

2.1.2 Cancer treatment options

Numerous cancer treatment modalities exist, broadly categorized as local and systemic treatments. Traditionally, common local treatments include surgery and radiotherapy, while common systemic treatments are chemotherapy, immunotherapy, endocrine therapy, and targeted therapy, with some overlap among the categories [22]. What constitutes the most appropriate treatment option depends on a variety of factors, including cancer type and stage. Most people diagnosed with cancer receive a combination of treatments, also referred to as multimodal cancer therapy [22]. Whether patients are treated with curative or palliative intent also influence treatment administration, as the purpose of palliative treatments is to control the cancer and relieve symptoms and side-effects for as long as possible.

Different treatments can be administered as primary treatment, adjuvant treatment, and neoadjuvant treatment. Surgery is most often performed as the primary treatment for solid tumours [22]. The purpose of the surgery is to remove as much of the cancer as possible while preserving the function of surrounding tissue, and is most effective at early-stage disease [22]. Neoadjuvant refers to treatments that are administered before primary treatment to control or shrink the tumour(s) and, in some cases, facilitate the effects of surgery. Adjuvant refers to

treatments that are administered in addition to, often after, the primary treatment to reduce the chance of cancer recurrence by destroying any remaining cancer cells or to improve the effect of e.g. radiotherapy. Most often, neoadjuvant and adjuvant therapies include chemotherapy, radiation therapy, hormone therapy, and/or immunotherapy [22].

However, the oncological landscape is rapidly changing with more than 50% of ongoing medical treatment trials focusing on novel cancer treatments [23]. Thus, changes to the modality and administration of different treatments will likely emerge as science advances, further impacting side-effects, late-effects, survival, and life beyond cancer. For example, the advent of new treatments such as immunotherapy for cancers resistant to other forms of treatment, has improved survival among patients with previously poor life expectancy, now living for years often on continuous treatment [24].

2.1.3 Cancer late-effects

Side-effects of cancer treatment are usually classified as acute when seen under treatment or within weeks after treatment, while late-effects have a longer-term presence [25]. Late-effects can be defined as health impairments that emerge post cancer treatment, sometimes months or even years after treatment has ended [25]. However, the onset, nature, and duration of late-effects may vary significantly.

Although the purpose of the treatment is to eliminate or destroy cancer cells, most traditional treatments will often impact healthy tissue as well. Surgical procedures may include the removal of reproductive organs affecting fertility, hormones, and sexual function, or removal of lymph nodes causing lymphedema through accumulation of lymphatic fluid. Chemotherapy primarily impairs cell division that are often rapid among cancer cells, but also occurs in non-cancerous cells. Thus, chemotherapy can have a toxic effects on healthy tissues leading to peripheral nerve damage and pain [26]. Radiotherapy aims to maximize the cytotoxic properties relative to what adjacent tissue can tolerate from radiation injury [27]. Nonetheless, some healthy cells are typically affected, and, in rarer cases, secondary malignancies can develop years after receiving radiotherapy [28, 29].

Physical late-effects can include cognitive impairments, musculoskeletal disorders, fatigue, reduced endocrine function, lymphedema, infertility, sexual dysfunction, cardiovascular disorders, neuropathy, and secondary malignancies

[28]. Musculoskeletal disorders and fatigue are among the most commonly reported physical late-effects, affecting around 50% of cancer survivors across various cancer types [28]. Psychological late-effects can include distress, anxiety, depression, post-traumatic stress disorder, and social impacts such as changes in relationships and social contact. Approximately half of cancer survivors report non-clinical depressive symptoms at some point during their cancer trajectory, with a higher prevalence among females [28].

2.2 Physical activity

Physical activity is defined as any bodily movement produced by skeletal muscles resulting in energy expenditure [30]. In the present thesis, the term "physical activity" will be used to represent all forms of physical activity including exercise. "Exercise" will be used when referring specifically to physical activities that are planned, structured, and repetitive, and have the intention of improving or maintaining physical fitness [30]. Time spent in different physical activity intensities can be estimated through energy expenditure, with levels >1.5 times greater than resting commonly defined as physical activity [31]. This relative energy expenditure can be referred to as metabolic equivalents (METs). Behaviours with METs ≤1.5 are commonly termed sedentary, METs >1.5 <3 as light intensity physical activity, METs 3-6 as moderate intensity physical activity, and METs >6 as vigorous intensity physical activity [31].

Various methods can be employed to estimate physical activity levels, with the choice depending on the research aim, study design, sample, and available resources. Self-report methods have a low participant burden and are often feasible to distribute to large samples, can register type of activity, requires few resources, can be use in studies with short timeframes, and when participants are spread out geographically. However, self-report methods are susceptible to biases such as difficulty in recalling all relevant activity, false responses caused by perceived expectations, and challenges in distinguishing between different intensities [32, 33].

Device-based monitoring, often referred to as objective measures, is considered more accurate compared to self-reported measures for estimating time in different physical activity intensities [33, 34]. The use and accessibility of

wearable devices, for both researchers and consumers, have increased tremendously the past decades due to technological advances. Devices are now easier to wear, more affordable, and can contain numerous sensors in addition to accelerometers [35]. Wearable devices can reduce or eliminate the biases associated with recall, social desirability, and differentiating between intensities, but can still be influenced by participants altering their normal routines due to study participation.

During the development of wearable devices, accelerometers, and reduction algorithms, it has become evident that the validity of physical activity estimates obtained from the devices is depended on various factors [36]. These include the decision rules defined by researchers (e.g., the wear-time protocols encompassing the number of hours each day and number of days the device is worn), the degree to which participants adhere to these rules, and the transformation of raw data to physical activity estimates [36].

In 2005, Mâsse et al., highlighted the lack of a standardized method for processing and reporting accelerometer data, with significant variability in decision rules applied across studies [36]. This variability impacted outcome variables, and the researchers concluded that comparisons of findings across studies would remain difficult until proper guidelines were developed [36]. Several years later, there is still debate and no consensus regarding the applied methods for handling device-based physical activity estimates [37, 38]. Appropriate methods for collecting and processing device-based physical activity estimates in cancer populations are even less explored, with many studies not report adequate information to interpret the applied wear-time protocols [35].

Although standardized algorithms for transforming raw physical activity data have been developed, their application varies widely between studies. Some devices depend on “black box” algorithms developed by the manufacturers whose specifics are undisclosed to researchers [38]. The use of such algorithms necessitates validation through research, but the evolving features of the devices make it challenging to compare results and establish a universal approach.

Developing standardized wear-time protocols might be more feasible, but requires accurate devices, minimal standard errors, study samples with consistent variability in physical activity levels who are representative of the population, and minimal bias effect on the variance. Standardization of wear-time protocols

could ensure reliable estimates across studies, but should also be developed as it is neither resource-efficient nor ethical to apply monitoring protocols that are unnecessarily long. Long and demanding monitoring protocols have been found to reduce protocol compliance and lead to exclusion of participants, thus reducing statistical power and external validity [38, 39].

Moreover, measurement precision is important for reducing the standard error of the estimates and the risk of making a type 2 error. Longer daily monitor wear-time reduces variability in estimates caused by capturing only small proportions of the day, leading to increased precision and reduced standard error, thereby reducing the required number of monitoring days [38]. To limit the standard error even more, Bergman and Hagströmer found that despite how may hours a device was worn each day, most reduction in standard error was achieved when the number of participants was increased as opposed to increasing the number of monitoring days (i.e., number of repeated measures within individuals) [37]. In sum, these findings suggest that with long daily wear-time and many rather than few participants, a monitoring period can be shortened [37, 38, 39]. Applying a shorter monitoring protocol may have the potential to improve study compliance supporting statistical power, and be more cost effective. However, the precise length of a valid monitoring protocol my differ across populations (e.g., diseased, and health individuals) due to different physical activity patters impacting the variability in physical activity levels. Thus, data collection and processing criteria should be population-specific when possible [38]. As standards for physical activity monitoring is less explored in cancer populations, there is a need to develop protocols specifically relevant to cancer survivors, and rely on results from this population rather than solely adopting protocols from other groups [35].

2.2.1 Recommendations

Cancer associations worldwide recommend that cancer survivors engage in physical activities with moderate-to-vigorous intensity (MVPA) for ≥150 minutes per week, including muscle strengthening exercises at least twice a week [40, 41]. Failing to reach this recommendation is defined as inactivity [31].

The heterogeneity of the cancer population is reflected in their physical activity levels. The proportions of cancer survivors reaching the recommended level of ≥150 minutes MVPA weekly differs across cancer types, subgroups, and measurement methods [34, 40, 42, 43]. Adherence to the guidelines has been

reported for approximately 30-60% of breast, colorectal, and prostate cancer survivors [42, 43], while as few as 20% adherence has been found among endometrial cancer survivors [40]. Higher levels of MVPA measured by a wearable device, have been found in cancer survivors who are younger, male, normal-weight, have lower levels of fatigue, higher educational levels, and fewer comorbidities [44]. Conversely, more sedentary time have been found among cancer survivors who are older, male, obese, smokers, more fatigued, closer to diagnosis, and treated with surgery, radiotherapy, and chemotherapy [44].

Although the impact of physical activity on cancer risk has been explored since the 1980s, the first exercise guidelines developed specifically for cancer survivors were published in 2010 [45]. At that time, evidence primarily from breast and prostate cancer survivors had indicated that physical activity not only reduced the risk of cancer but was also safe and well-tolerated during and after treatment, with potential improvements in health outcomes. Since the 2010 guidelines, the number of RCTs within exercise oncology has increased by several fold, leading to guideline updates [41, 46]. A summary of this evidence has found consistent benefits of physical activity after diagnosis for late-effects such as anxiety, depressive symptoms, fatigue, health related quality of life, upper extremity breast cancer-related lymphedema, and physical function [41]. Moderate evidence also supports the positive effects on bone health and sleep, while lower mortality risk is observed in the most active breast, colorectal, and prostate cancer survivors compared to the least active [41, 46]. However, limited evidence is currently available on the impact of post-diagnosis physical activity on survival. There are also persistent gaps in our understanding of the underlying biological mechanisms linking physical activity to development and progression of cancer, and the majority of the evidence is still based on selective samples of the most common cancer types [46].

As previously mentioned, cancer survivors vary in demographics, prognosis, treatment options, and associated late-effects. To participate in exercise RCTs, cancer survivors must typically meet specific eligibility criteria, such as age, number or type of comorbidities, and physical ability [41]. One of the reasons for this is that there is limited evidence regarding safe and suitable exercise programs for underrepresented subgroups. In understudied subgroups such as individuals with advanced cancer, older adults, ethnic minorities, and individuals with less educated backgrounds, information about exercise intervention benefits,

feasibility, and safety, is lacking [41, 47]. Efficacy studies may also not choose to tailor the exercise to individual needs as the exercise amount and volume must be standardized for the intervention. This often results in samples that are healthier, with higher physical function and exercise motivation [41]. When the purpose of explanatory trials is to assess the effect of exercise on a specific outcome, the participants are recruited based on the presence of this outcome. This increases the selection bias further, especially if secondary outcomes are assessed or participants are lost to follow-up [48]. Thus, the external validity and applicability of findings in explanatory trials can be poor [4, 41]. Interventions with low adherence to the exercise (in some subgroups) may not be suitable for widespread implementation, despite observations of significantly improved outcomes [10]. Thus, adaptations of programs that have demonstrated efficacy are needed in order to reach vulnerable groups [49]. However, the current evidence base has accumulated sufficient evidence to assume that, among survivors of early-stage but less studied cancer types without unique safety concerns, the efficacy of physical activity on various outcomes would be similar to what has been found in breast and prostate cancer survivors [41]. The conclusion from the 2010 exercise guidelines that exercise and physical activity are generally safe for cancer survivors remains unchanged based on the majority of studies conducted since [41]. There is enough evidence to integrate physical activity and exercise into clinical care and follow-up for the majority of cancer survivors, and several calls to action have been issued since the 2010 guidelines were first published [10, 50, 51, 52]. Compared to the amount of explanatory trials assessing the effects of physical activity, the amount of pragmatic trials focusing on program feasibility, how to incorporate physical activity behaviour change into routine care, and promotion of long-term physical activity behaviour change, are scant [10, 53]. This should be considered before scaling up interventions or determining exercise prescriptions to deliver in the cancer care.

2.3 Self-management

The cancer care and follow-up should enable and support cancer survivors to self-manage their health, including performance of behaviours such as physical activity that can positively affect their health and wellbeing long-term. Self-management have several definitions, and no consensus exists for a comprehensive definition [54]. Among individuals with chronic conditions, including cancer, self-management can translate to a dynamic and continuous

ability to i) manage the disease or condition including its physical and psychological symptoms and consequences, ii) adhere to required treatments, iii) recognize and report signs of disease progression, iv) seek support when appropriate, v) and make lifestyle changes to promote health, wellbeing and survival [55, 56]. Self-management support is described as support delivered through healthcare services to aid and encourage people living with long-term conditions to manage and improve their health and wellbeing [57]. The purpose of self-management support can be to reduce or eliminate a health issue, but it can also include changing the perception of an issue, such as making it less bothersome [57]. As part of self-managing one's health, physical activity behaviours can be performed, adjusted, and otherwise controlled by the individual based on their prerequisites, circumstances, and fluctuations in health.

Foster & Fenlon (2011) developed a model to specifically illustrate the complexity of providing targeted self-management support that accounts for the individual characteristics of cancer survivors (Figure 1). The model recognizes that people have different dispositions, support and resources, self-efficacy, and need for support. It has long been recognized that there is considerable variation in how individuals respond to objectively similar stressful life-events, such as a diagnosis and treatment for cancer (Bandura, 1977; Lazarus & Folkman, 1984). This was recently confirmed by researchers who found that both personal resources and perception of stressors impacted stress response, which in turn strongly predicted depression (Obbarius, Fischer, Liegl, Obbarius, & Rose, 2021). These findings confirm the assumption that stress is a highly individual concept arising from a person-environment transaction (Lazarus & Folkman, 1987; Obbarius et al., 2021).

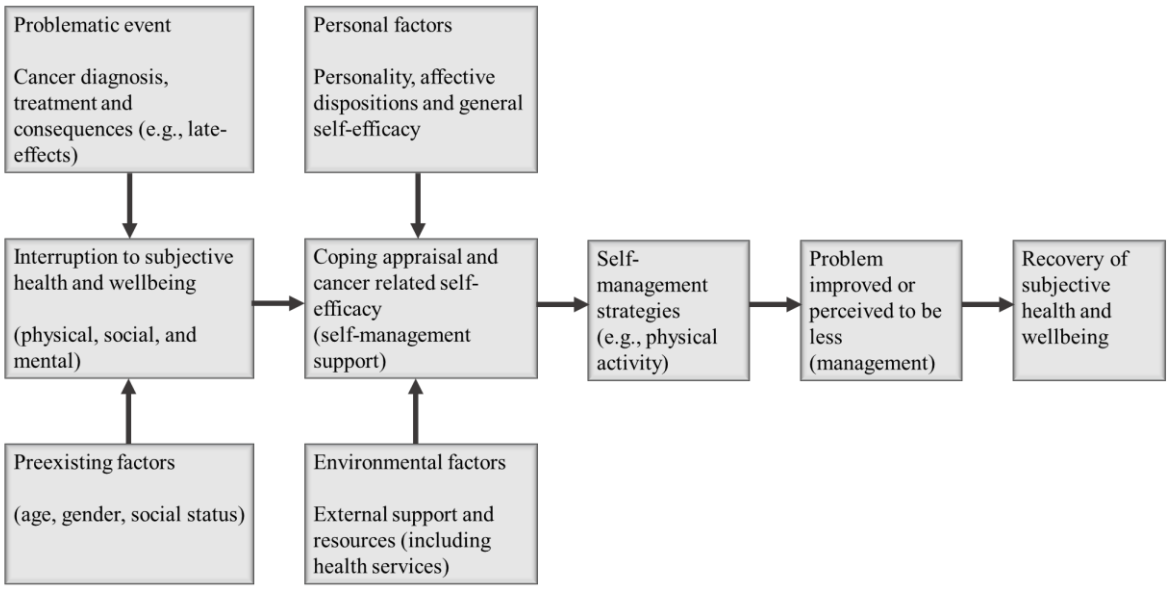


Figure 1. Figure adapted from Foster and Fenlon (2011) illustrating the complexity of providing targeted self-management support accounting for the individual characteristics of cancer survivors.

The model by Foster and Fenlon (2011) has two assumptions: i) a cancer diagnosis and treatment disrupt an individual's subjective sense of health and wellbeing, and ii) this disruption can be restored over time, although not necessarily to the same level as pre-diagnosis [57]. The model is designed to include the wider domains of health and wellbeing that may impact self-management. However, the developers note that their research suggests that self-efficacy is a key factor enabling cancer survivors to manage problems following treatment into recovery [57]. In the model, the cancer diagnosis, treatment, and related negative effects are viewed as the *problematic event* (Figure 1). This, combined with preexisting factors such as age, gender, and social status, influence how disruptive the diagnosis and treatment are perceived and to which degree health and wellbeing are affected. How the cancer survivor appraises the situation, and their preparedness to tackle it are further influenced by personal factors such as general self-efficacy and environmental factors like social support. These individual appraisals determine the type of self-management strategies to employ. The chosen strategies, in turn, affect whether the *problem* is effectively managed and possibly improved, ultimately influencing the recovery of subjective health and wellbeing [57]. While this model primary focuses on subjective health and well-being, it may be argued that applying appropriate self-

management strategies targeting individual health impairments may also lead to improved objective health outcomes.

2.3.1 Physical activity behavioural change

Self-management involves making lifestyle changes to promote health, wellbeing and survival [55, 56]. Such lifestyle changes, including improved physical activity levels, requires components of behavioural change [8]. For example, self-management support improving the ownership and responsibility for one's health may be necessary to attain the long-term benefits of physical activity. To develop implementable self-management interventions that facilitate physical activity, it is necessary to first understand how health and wellbeing is restored over time through increased physical activity and identify those who are more likely to require support [57, 58]. Subsequently, what forms the self-management support should take can be addressed.

Knowledge about how interventions work and cause behaviour change is important during their development [59]. Interventions grounded in relevant theories, utilizing key concepts causally related to behaviour, have the potential to achieve stronger effects and contribute more to behavioural science [59]. Interventions based on self-efficacy and perceived competence which are key concepts in the self-determination theory, have in meta-analyses been found to positively impact depression, social outcome, objective physical outcomes, and quality of life among cancer survivors [60]. However, few have investigated whether such interventions impact physical activity behaviour [60].

The "active ingredients" of behaviour change interventions, theorized to bring about change (e.g., self-monitoring or goal setting), are referred to as behaviour change techniques [61]. Behaviour change techniques are specific, observable, and replicable components of an intervention or program, designed to alter or redirect habitual patterns of behaviour. These techniques have been structured and categorized to provide researchers and practitioner with standards for reporting intervention content [61]. This enhances the comparability and replication of interventions, the identification of techniques associated with desirable outcomes, and supports the development of behaviour change theories. However, it has been argued that the behavioural change effects of such techniques depend on the specific conditions or settings under which they are applied [62, 63]. Meta-analyses reporting the effect-sizes of different behaviour change techniques rarely account for the different contexts under which the

technique was applied, although the development of effective interventions is more complicated than inferring effectiveness from techniques based on differences in effect-size [63]. The components and contexts that are crucial for adequate analysis of intervention content, effectiveness, and for future design and implementation of interventions, should be accounted for. Not accounting for contextual factors can hamper a study's contribution to behaviour science by promoting partial, thus incorrect, application of theory and effectiveness [63]. As factors inside and outside of the individual affect the perception of the problematic event, self-efficacy, and appropriate self-management strategies, these factors must be reported (Figure 1). Thus, assessments of behaviour change interventions aiming to facilitate physical activity participation require more than the reporting of behaviour change techniques.

2.4. From exploration to implementation

Widespread implementation and accessibility of exercise programs and proactive self-management support in the cancer care remains deficient, despite the call for more pragmatic trials of clinically integrated exercise programs and physical activity facilitation a decade ago [8, 10, 53, 64]. Reasons for the lack of initiative and implementation may be insufficient policies and prioritization of resources, but likely also the limited proportion of research dedicated to implementation [8, 53].

To implement services delivered by humans is an intricate process because the services are delivered through the actions of individuals and organizations which exist within complex, multilayered social contexts [11, 65]. Recent research has identified specific barriers and facilitators of physical activity program implementation in the cancer care [66]. Exercise programs tailored to various needs and capabilities was proposed as the first step towards successful implementation, as cancer survivors have reported that programs not suiting their needs discourage them from joining [66]. Bringing together peers was also suggested to facilitate implementation and program adherence through a sense of belonging [66]. Additionally, barriers for implementation included cancer survivors with lack of responsibility for their health, non-involvement of the general practitioner, and poor communication between the secondary and primary healthcare [66, 67].

Implementation in the healthcare setting involves the translation of research into effective practices [11]. Numerous models displaying factors affecting this translation of evidence have been proposed, and one such model is the Exploration, Preparation, Implementation, and Sustainment (EPIS) framework (Figure 2). The EPIS framework is a parsimonious model displaying the recursive process of the four phases and two-way relationships between each connected phase [11]. An essential link in the connection between research (exploration) and practice (implementation) is the translation (preparation) of research into broader application and impact.

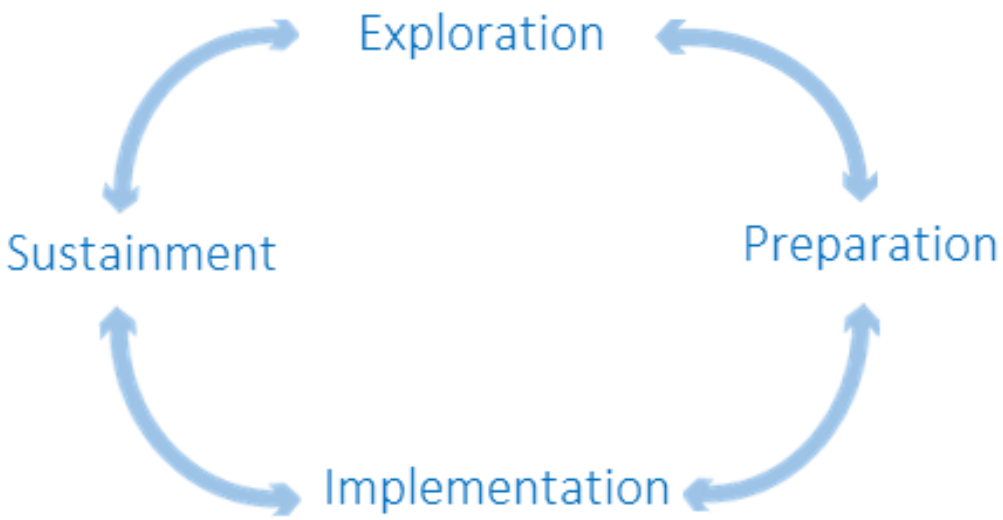


Figure 2. The EPIS model displaying the process of Exploration and Preparation to Implementation and Sustainment. Figure adapted from Aarons et al. (2011).

For many years, the path from science to service was seen as a passive process involving dissemination and delivery of information that somehow researched enlightened leaders and practitioners, who then put the innovations into practice [65]. With this approach, researchers do their part by publishing their findings, while deliverers fulfil their role by reading the literature and making use of the innovations in their work with the respective population. In the cancer care context, this has largely been the prevailing practice for facilitating physical activity participation among cancer survivors [53]. It has primarily fallen upon oncologists or health care professionals to educate themselves on the benefits of physical activity, promote relevant practices, and device strategies for improving

activity levels. Unfortunately, this approach has not resulted in higher physical activity levels nor widespread implementation of physical activity and exercise in the cancer care [53].

2.5 Knowledge gaps

While there is consensus regarding the significant benefits of physical activity on health and wellbeing among cancer survivors, further research is imperative to implement physical activity and exercise as an integrated part of comprehensive cancer survivorship care [8, 10, 46]. This necessitates the translation of evidence from explanatory trials into pragmatic research relevant for real-world settings. Nonetheless, several critical topics remain understudied.

There is little standardization of device-based physical activity monitoring in cancer populations, and applied wear-time protocols are often insufficiently reported [35]. This limits the ability to make conclusions about appropriate wear-time and highlights the need for developing standards for measuring. To the author's knowledge, no study has previously explored the minimum monitoring period leading to reliable physical activity estimates in a mixed sample of cancer survivors.

Explanatory trials assessing the effects of physical activity and exercise interventions are prone to including selective samples, and observed effects may not be generalizable to all cancer populations [41, 47]. Dropout from the interventions may increase selection bias and be an indicator of poor feasibility and lack of broad applicability, highlighting the need for targeted support among cancer survivors. To the author's knowledge, no study has previously utilized individual patient data from exercise RCTs to assess intervention dropout and its effect on external validity.

There is an urgent need for improvements in physical activity participation within cancer populations and physical activity facilitation through self-management support in the cancer care [8, 58]. To achieve this, self-management skills related to physical activity behaviours must be explored, and vulnerable and less studied subgroups should be targeted. This can both support the identification of effective components of self-management for testing and possible implementation, and improve comparability of intervention content and effects across studies. To the author's knowledge, there have been few

assessments of self-management constructs relevant for physical activity participation among gynaecological cancer survivors.

2.6 Aims and objectives

The overarching aim of the present thesis was to explore unaddressed areas in the literature and close research gaps related to methodological components of studies measuring and promoting physical activity and exercise in cancer populations. Methodological components related to populations, measurement tools, outcomes, and methods that can inform further research and facilitate the next step towards *Implementation* of physical activity in the cancer survivorship care have been addressed. Thus, the present research reflects the *Preparation* phase of the EPIS model and support the translation of knowledge from explanatory trials into relevant evidence for further design of pragmatic trials. Three objectives were defined.

The objectives were:

1) To obtain the minimum monitoring period required for reliable estimates of device-based physical activity levels among cancer survivors (Paper I). The purpose of this objective was to enhance the standardization of physical activity monitoring across studies, thereby improving accuracy and comparability of estimates.

2) To assess participant and intervention characteristics associated with dropout from exercise interventions (Paper II). The purpose of this objective was to investigate the impact of dropout on the external validity of exercise RCTs and identify subgroups of cancer survivors who may require additional support to complete exercise programs.

3) To assess self-management skills associated with physical activity participation among gynaecological cancer survivors (Paper III). The purpose of this objective was to identify self-management skills to target in intervention studies to facilitate physical activity behaviour change in this population.

3 Materials and methods

3.1 Sample

Three different samples were assessed in relation to the three objectives in the current thesis. Data from 984 cancer survivors were assessed when addressing the first objective, 2467 when addressing the second objective, and 1433 when addressing the third objective (Table 1). In total, these samples constituted 4884 cancer survivors from 11 countries, participating in 37 different original trials. The countries (n trials) represented were the Netherlands (8), USA (8), Australia (7), Canada (4), Germany (4), Norway (3), United Kingdom (2), Sweden (1), Denmark (1), New Zealand (1), and Spain (1). The cancer survivors analysed as part of this thesis were, or had been, treated with curative intent.

Table 1. Descriptive characteristics of all cancer survivors and individual studies analysed as part of this thesis across the three objectives and to address each objective.

	Characteristics of all participants n=4884	**Characteristics of participants analysed for each objective**		
Participant characteristics		**Paper I** Phys-Can CRC-NORDIET n= 984	**Paper II** POLARIS n=2467	**Paper III** InCHARGE n=1433
	Mean (SD)	**Mean (SD)**		
Age (years)	58.3 (12.6)	62.9 (10.9)	54.7 (11.4)	62.4 (13.6)
BMI (kg/m^2)	27.1 (5.4)	26.2 (4.5)	27.1 (5.1)	27.7 (6.2)
	n (%)	**n (%)**		
Total number of participants	4884 (100)	984 (100)	2467 (100)	1433 (100)
Participating in study				
During treatment	1786 (36.6)	532 (54.1)	1254 (50.8)	-
After treatment	3095 (63.4)	452 (45.9)	1210 (49.1)	1433 (100)
Missing	3 (0.1)	-	3 (0.1)	-
Sex				
Female	3987 (81.6)	627 (63.7)	1927 (78.1)	1433 (100)
Male	879 (18.0)	339 (34.5)	540 (21.9)	-
Missing	18 (0.4)	18 (1.8)	-	-

Cancer type					
Breast	2158	(44.2)	414 (42.1)	1744 (70.7)	-
Gynaecological	1433	(29.3)	-	29 (1.2)	1433 (100)
Gastrointestinal	614	(12.6)	473 (48.1)	141 (5.7)	-
Male genitourinary	402	(8.2)	88 (8.9)	314 (12.7)	-
Haematological	199	(4.1)	-	199 (8.1)	-
Missing/other	78	(1.6)	9 (0.9)	40 (1.6)	-
Educational level					
Low-medium	2672	(54.7)	410 (41.7)	1146 (46.5)	1116 (77.9)
High	1838	(37.6)	527 (53.6)	1003 (40.7)	308 (21.5)
Missing	374	(7.7)	47 (4.8)	318 (12.9)	9 (0.6)
Weight status					
BMI <18.5	42	(0.9)	12 (1.2)	16 (0.6)	17 (1.2)
BMI 18.5 <25	1787	(36.6)	387 (39.3)	832 (33.7)	548 (38.2)
BMI 25 <30	1610	(33.0)	367 (37.3)	793 (32.1)	431 (30.1)
BMI ≥30	1128	(23.1)	167 (17.0)	544 (22.1)	415 (29.0)
Missing		-	-	282 (11.4)	22 (1.5)
Study characteristics					
Study					
Phys-Can	532	(10.9)	532 (54.1)	-	-
CRC-NORDIET	452	(9.3)	452 (45.9)	-	-
POLARIS	2467	(50.5)	-	2467 (100)	-
InCHARGE	1433	(29.3)	-	-	1433 (100)
Country					
The Netherlands	1307	(26.8)	-	760 (30.8)	547 (38.2)
Norway	888	(18.2)	452 (45.9)	49 (2.0)	387 (27.0)
Australia and New Zealand	571	(11.7)	-	571 (23.1)	-
Sweden	532	(10.9)	532 (54.1)	-	-
Denmark	499	(10.2)	-	-	499 (34.8)
USA	429	(8.8)	-	429 (17.4)	-
Canada	309	(6.3)	-	309 (12.5)	-
Germany	182	(3.7)	-	182 (7.4)	-
United Kingdom	159	(3.3)	-	159 (6.4)	-
Spain	8	(0.2)	-	8 (0.3)	-

SD – standard deviation; IQR – inter quartile range; BMI – body mass index; Phys-Can – the Physical Training and Cancer study; CRC-NORDIET – the Norwegian dietary guidelines and colorectal cancer survival; POLARIS – Predicting Optimal cancer Rehabilitation and Supportive care; InCHARGE – the International Collaboration of Healthcare professionals and Researchers for Gynaecologic Cancer Survivors' Empowerment study

3.2 Paper I

3.2.1 Study design and sample

To address the first objective, data from the two studies Physical Training and Cancer (Phys-Can) and the Norwegian Dietary Guidelines and Colorectal Cancer Survival (CRC-NORDIET) was harmonized [68, 69]. Both studies applied the same wearable device for estimating physical activity with the same wear-time protocol. The Phys-Can study was conducted in Sweden and included survivors of breast, colorectal, and prostate cancer (n=532). The CRC-NORDIET study was conducted in Norway and included survivors of colorectal cancer (n=452). For the present study, participants adhering to the protocol of continuous monitoring (≥22 hours daily) for six days were identified in the harmonized sample. Of the total 984 participants, 736 (75%) complied with the initial monitoring protocol and were included in the reliability analyses. Data was obtained from the data manager of the respective study, and similar covariates were harmonized. Physical activity levels, as measured by the device, were calculated based on software developed by the manufacturer.

3.2.2 Objective measures of physical activity

In the Phys-Can and CRC-NORDIET study, the SenseWear™ Armband Mini (SWAM) (BodyMedia Inc. Pittsburgh, PA, USA) was used to obtain objectively measured physical activity estimates. The SWAM is a multi-sensor device that estimates energy expenditure further converted into time spent in different physical activity intensities through METs. The SWAM estimates energy expenditure based on data from a tri-axial accelerometer and sensors measuring heat flux, galvanic skin response, skin temperature, and near-body ambient temperature. SWAM is a smaller version of the former SenseWear Armband which has been found feasible and valid for use in cancer survivors [70, 71]. As the next generation model of this device, the SWAM has not been validated in the cancer population, but has shown the same accuracy as the former model, and is expected to be more convenient to use [72, 73]. The device was worn on the non-dominant upper arm of the participants. A seven-day protocol was applied in the Phys-Can and CRC-NORDIET studies. However, as the day of distributing SWAM was considered as the first monitoring day, this day showed inadequate wear-time and was excluded. Thus, the criterium for a valid monitoring period was set at ≥22 hours wear-time each day for six days, representing continuous

monitoring, only allowing short periods of non-wear-time, as the device could not be worn when in contact with water. With this protocol, absolute values for measures of physical activity could be used in the analyses. Time in different intensities was defined based on METs as previously recommended. METs >1.5 <3 represented light intensity physical activity, METs 3-6 moderate intensity physical activity, METs >6 as vigorous intensity physical activity, while all activity ≥3 METs were also reported as MVPA [31]. The variance in these intensities across the six-day period was further used in the reliability analyses to establish the minimum monitoring period.

3.3 Paper II

3.3.1 Study design and sample

To address the second objective, pooled data from the Predicting Optimal cancer Rehabilitation and Supportive care (POLARIS) study was assessed [74]. This dataset consisted of survivors of mixed cancer types from 34 exercise RCTs, where 2467 participants completed baseline and were randomized to the intervention arms of the studies and included in the present analyses. The primary objective of the POLARIS project was to conduct individual patient data meta-analyses to evaluate the effects of physical activity and psychosocial interventions on health related quality of life among cancer survivors, and identify moderators of these effects [74]. POLARIS was the first individual patient data meta-analysis conducted on these outcomes in cancer populations, and the collection of data from RCTs are continuously expanding to increase the pooled sample. The raw data shared by original RCTs were transferred using password-protected encryptions, and all data was anonymized by original investigators before transfer. Upon harmonization, summary statistics for all variables were sent back to collaborators to verify categories, unit measures, and comparing baseline characteristics with previous publications. Consistency of data within individuals was verified and highly potential outliers and missing data was identified. Any data queries were discussed and resolved directly with the responsible collaborating principal investigators [74]. The POLARIS data analysed in the present thesis were harmonized in 2017, with individual patient data from RCTs investigating exercise programs in relation to various outcomes. The trials were conducted between 2003 and 2016. A data sharing agreement had to be signed and approved to obtain the harmonized individual patient data. Only participants who completed baseline assessments were included in the present

analyses, and cancer survivors with metastatic disease or participants deceased during the study period were excluded from the analyses.

3.3.2 Defining dropout

The harmonized dataset consisted of baseline assessments (pre-intervention) and one timepoint for follow-up assessments (post-intervention). Intervention dropout was determined for participants who did not provide any data on the post-intervention follow-up. Some variables had missing values as they were not measured across all included studies, but variables were not included in analyses if missing data was more than 15%. However, all available variables were assessed to determine study dropout although not included.

3.3.3 Exercise intervention characteristics

In the POLARIS database, the 34 included RCTs were also harmonized based on some general intervention characteristics (Table 2). This allowed for exploration of interactions between participant characteristics and intervention characteristics when assessing associations with dropout.

Table 2. Characteristics of the 34 exercise interventions harmonized as part of the POALRIS database with a total of 2467 participants.

Intervention characteristics and description		**n (%) participants**	**n trials**
		Total=2467	Total=34
Intervention timing			
Time of intervention delivery was defined in relation to primary cancer treatment and was dichotomized into during or post-treatment.	During treatment	1254 (50.8)	17
	Post-treatment	1210 (49.1)	20
Intervention duration			
The prescribed duration of the exercise intervention was categorized based on tertiles.	≤3 months	828 (33.6)	13
	>3 ≤6 months	906 (36.7)	9
	>6 months	733 (29.7)	11
Exercise type			
Type of exercise performed and	Supervised aerobic	263 (10.7)	6

whether the exercise sessions were supervised or not was categorized into one variable. Exercise including both aerobic and resistance exercises were categorised as mixed. No unsupervised resistance exercise was performed.	Unsupervised aerobic	419 (17.0)	6
	Supervised mixed	808 (32.7)	12
	Unsupervised mixed	427 (17.3)	4
	Supervised resistance	550 (22.3)	9
Exercise intensity			
Exercise intensity was categorised from low to vigorous intensity using the definitions of the American College of Sports Medicine intensity [75, 76].	Low-moderate	167 (6.8)	2
	Moderate	857 (34.7)	13
	Moderate-vigorous	985 (39.9)	16
	Vigorous	195 (7.9)	2
Exercise session duration			
How long the exercise sessions were prescribed to last in minutes.	≤30 minutes	903 (36.6)	12
	>30 ≤60 minutes	1252 (50.8)	17
	>60 minutes	243 (9.9)	4
Exercise Session Frequency			
The prescribed frequency of exercise sessions weekly.	2	1307 (53.0)	19
	3	323 (13.1)	6
	4	199 (8.1)	2
	5	218 (8.8)	5
	6	-	-
	7	218 (8.8)	1

Percentages not adding up to 100 was caused by some missing data on individual participants. Participants in some studies performed different interventions, thus some descriptives may add up to more than 34 interventions.

3.4 Paper III

3.4.1 Study design and sample

To address the third objective, data from the International Collaboration of Healthcare professionals and Researchers for Gynaecologic Cancer Survivors' Empowerment study (InCHARGE) was analysed [77, 78]. This dataset included 1433 Norwegian (27.0%), Dutch (38.2%), and Danish (34.8%) survivors of

endometrial (n=699), ovarian (n=403), and cervical (n=331) cancer. The participants had been diagnosed with gynaecological cancer between January 2011 and December 2016, were 18 years of age or older, and were able to read and understand the first language of their respective country. In the Netherlands, eligible individuals were identified from the Netherlands Cancer Registry. In Norway, eligible individuals were identified by responsible doctors from six Norwegian departments of gynaecology who screened the electronic patient system. In Denmark, eligible individuals were identified from the Danish National Patient Registry. Data was collected between October 2018 and June 2019. All participants filled out the same questionnaire in their respective language.

3.4.2 Self-reported physical activity and self-management

The Health Education Impact Questionnaire (HeiQ) version 3 was used to assess self-management constructs, including physical activity participation [79]. The questionnaire was developed to provide direct and realistic measurements of the impact and quality of self-management support interventions to inform health professionals and leaders, health practitioners, policymakers, and researchers in their work [80]. No such specific, validated, and comprehensive questionnaire had previously existed and the HeiQ was considered especially relevant for the healthcare sector where resources are finite [79]. The 40 items of the HeiQ are score on a Likert-type scale ranging from 1 (strongly disagree) to 4 (strongly agree). The items are divided into eight scales containing 4-6 items, and a mean score for each scale is calculated with no items weighted (Table 3). Thus, the scale scores can be represented on the same four-point Likert scale. No global score is calculated across scales as the eight HeiQ scales were designed and validated to represent separate independent constructs or questionnaires that could be administered individually or as a panel of indicators [80]. A comparative fit index above 0.98 has previously been found for all the HeiQ scales [79]. A Cronbach’s alpha of 0.80 or higher has been reported for seven of the scales and 0.70 for Self-Monitoring and Insight [79]. The questionnaire has been validated in Dutch, Norwegian, and Danish populations [81, 82, 83]. The scales Social Integration and Support, Health Service Navigation, Constructive Attitudes and Approaches, Skill and Techniques Acquisitions, and Emotional Distress have previously been validated in a cancer population [84].

The scale measuring Health Directed Activity was used as a measure of physical activity participation and whether physical activities and other healthful activities were performed to improve health and wellbeing [79]. The other seven scales representing independent self-management constructs were assessed in relation to physical activity participation.

Table 3. List of the Health Education Impact Questionnaire scales as described by Osborne, Batterham, and Livingston (2011).

Health Directed Activity Focusing on healthful behaviours such as, walking, exercise, and relaxation. The scale accounts for the level of functional activity incorporated into the lifestyle. The scale was designed to detect small but tangible improvements in physical activity or exercise for interventions aiming to improve such outcomes.
Positive and Active Engagement in Life Focusing on engagement in life and positive affect. The scale embodies the notion of engaging in life-fulfilling activities ("things I really like"). It includes both behavioural elements (participation in life activities) and psychological elements (enthusiasm for life activities).
Emotional Distress Focusing on health-related negative affect like anxiety, stress, anger, and depression. The scale measures negative affective responses to illness. The items of this scale is reversed so that a lower score represent more emotional distress and a higher score reflects more emotional wellbeing.
Self-Monitoring and Insight Focusing on self-monitoring, setting reasonable targets, and having insight into living with a health problem. The scale captures how an individual engages in self-monitoring of their condition. An important component is the acknowledgement of, and possession of, realistic disease-related limitations and the ability and confidence to adhere to these limits. This may also include monitoring of specific subclinical indicators of disease status.
Constructive Attitudes and Approaches Focusing on positive attitudes, sense of control, and empowerment. The scale is embodied in the statement "I am not going to let this disease control my life" and includes a shift in how individuals view the impact of their condition on their life.
Skill and Technique Acquisition Focusing on symptom relief skills, and skills and techniques to manage own health. The scale aims to capture knowledge-based skills and techniques

(including the use of equipment) that participants utilize to help them manage disease-related symptoms and health problems.

Social Integration and Support
Focusing on feelings of social isolation because of the illness, sense of support, and seeking support from others. The scale aims to capture the positive impact of social engagement and support that evolves through interaction with others. It also involves the confidence to seek support from interpersonal relationships as well as from community-based organizations.

Health Service Navigation
Focusing on communication, decision processes, and relationships with health professionals. The scale is concerned with the individual's understanding and ability to confidently interact with a range of health organizations and health professionals. It measures the confidence and ability to communicate and negotiate with health care providers to have needs met.

3.5 Shared measures

3.5.1 Demographic characteristics

Commonly reported person characteristics were available for most cancer survivors across the included samples. Data on sex (male, female), age (years), weight status expressed as body mass index (BMI), and educational levels was available for all participants. Other characteristics were partner status, employment, and country of residence, included in the analyses of objective three. Although educational level was reported across the samples, there were some differences in how the categories were defined. BMI was expressed as kilogram body weight divided by height in meters squared (kg/m^2). In Phys-Can and CRC-NORDIET (Paper I) and POLARIS (Paper II), educational level was harmonized and dichotomized into low-medium and high education. In Paper I, low-medium education included primary and secondary school while high education included education at college and university level. In Paper II, educational level was dichotomized into participants with college or university education, and participants without college or university education. Higher vocational studies were included in the high education category. In InCHARGE (Paper III), educational level was categorized into four groups. Highest completed education at primary school or less was categorized as primary or lower education, vocational school (1-2 years) was categorized as secondary education, completed high school was categorized into medium education, while education at college or university level was categorized as high education. When

summarizing the characteristics of participant across the studies in the present thesis, educational levels from the InCHARGE study was dichotomized into having education at college or university lever, or not.

3.5.2 Cancer specific characteristics

Cancer type was reported in all included samples and adjusted for in analyses. Information on cancer stage was only available for participants in the InCHARGE study and included in analyses in Paper III. As the InCHARGE participants were all diagnosed with gynaecological cancer, cancer stage was defined in line with the FIGO (Federation Internationale de Gynecologie et d'Obstetrique) criteria and reported as stage I, II, III, IV without substages. Information on cancer treatment was not available or insufficiently harmonized across samples. When information on treatment type was available, it was highly correlated with cancer type, where some cancer types were more likely to have certain combinations of treatment modalities. For example, both breast and prostate cancer survivors may receive hormone therapy, however the type of drug, mechanisms of action, associated side-effects, and treatment duration differ significantly based on the respective tumour type. Thus, treatment type was not included in analyses. In the POLARIS data, information about whether participants were on treatment or had finished treatment was included. Individual patient data on time (months) since diagnosis was assessed in the InCHARGE sample.

3.6 Statistical analyses

3.6.1 Comparing means and distributions

Differences in continuous variables between two groups were assessed using independent sample t-tests, and between more than two groups using the one-way ANOVA, and were reported as p-values. For categorical variables, p-values for differences across groups were reported based on the chi-square tests. Differences were considered statistically significant for p-values <0.05.

The magnitude of differences in covariates between intervention dropouts and completers in Paper II, and between tumour types in Paper III, were determined based on measures of effect-size. In these respective contexts, differences between groups were considered relevant in the interpretation of the main results,

hence the reporting of effect-sizes. Common cut-offs for magnitude of effects were reported to ease interpretation.

Cohen's d was used as the measure of effect-size when there were two groups and a continuous covariate. Cohen's d can be interpreted as a percentage of the standard deviation, such that a value of 0.5 represents a difference in the covariate equal to half of the standard deviation [85]. Values <0.2 was considered negligible, values ≥0.2 to <0.5 were considered small, values ≥0.5 to <0.8 were considered medium, and values ≥0.8 were considered large effect-sizes [85].

Eta-squared was used as the measure of effect-size when there were more than two groups, and the covariate was continuous. The Eta-squared can range from 0 to 1, and values <0.01 were considered negligible, values ≥0.01 to <0.06 were considered small, values ≥0.06 to <0.14 were considered medium, and values ≥0.14 were considered large effect-sizes [86].

Cramer's V was used as the measure of effect-size when the covariates were nominal. Cramer's V can range from 0 to 1, and values <0.1 were considered negligible, values ≥0.1 to <0.2 were considered small, values ≥0.2 to <0.4 were considered medium, values ≥0.4 to <0.6 were considered medium-large, and values ≥0.6 were considered large effect-sizes [86].

Kendall's tau b was used as the measure of effect-size when the covariate was ordinal. Kendall's tau b can range from -1 to 1. Values (±) <0.1 were considered negligible, values ≥0.1 to <0.2 were considered small, values ≥0.2 to <0.3 were considered medium, and values ≥0.3 were considered large effect-sizes.

3.6.2 Paper I

To obtain the minimum monitoring protocol for reliable physical activity estimates, the six monitoring days were assessed with the intra-class correlation coefficient (ICC). The ICC is a measure of the relative proportion of total variance contributed by the between subject variances. Thus, a higher ICC value represents larger between subject variance in physical activity and lower within subject variance or day-to-day variation in physical activity. A higher ICC suggests that a shorter monitoring period is reliable, and an ICC ≥0.8 was in the present study used as the cut-off for reliable estimates [87].

As several versions of the ICC exists, researchers have recommended that versions are compared before choosing the most appropriate model to use [88].

Similar ICC values across versions suggests that there is low impact of bias on the variance in the estimates. Thus, after comparing models with the present physical activity estimates, the most parsimonious version of the ICC analyses was applied (the one-way random). The ICC value based on the six days variance was obtained for light intensity, moderate intensity, vigorous intensity, and MVPA, representing the reliability of using one monitoring day to represent the six-day period. To obtain the ICC of using and increasing number of days to represent the monitoring period, the Spearman Brown formula was applied for each intensity. The formula assesses interrater reliability, where a monitoring day in the present study represents a rater. Thus, the formula calculates the ICC value when data from an increasing number of raters are averaged. The formula is expressed as $((k \times r) \div (1 + (k - 1) \times r))$ where k represents the number of raters (monitoring days) averaged, and r is the initial ICC obtained from the one-way random analysis. The ICC one-way random and Sperman Brown formula was also performed within subgroups.

As measures of activity level, mean minutes spent in the different physical activity intensities and relative energy expenditure were presented and compared. Relative energy expenditure was calculated as total energy expenditure as measured by the SWAM, divided by basal metabolic rate calculated with the Mifflin St. Jeor formula accounting for sex, body mass, and age [89]. The result of this equation is commonly referred to as a value for physical activity level (PAL value) [90, 91]. It is recommended that individuals achieve a PAL of 1.75 or greater. The number of participants reaching the recommended 150 minutes MVPA weekly and the recommended PAL value of 1.75 was compared.

3.6.3 Paper II

To assess which participant and exercise intervention characteristics were associated with intervention dropout, a decision tree model was applied. The choice of method was based on the large sample, the binary outcome, great number of relevant covariates, and many possible interactions across participant and intervention characteristics. The decision tree algorithm can assess a large number of variables simultaneously and provides additional information about the combined effects of the covariates. The conditional inference tree (Ctree) was applied as this tree chooses variables for splitting based on a significance level (p-values <0.05) [92, 93]. Significant associations are determined by a permutation-based conditional inference test, and the covariate with the smallest

p-value from this test is used for splitting. For binary covariates chosen for splitting, the predefined categories of the variable are split. For covariates with more than two categories, the algorithm searches for the combination of categories that yields the smallest p-value and makes a binary split of collapsed groups. For continuous covariates, the algorithm split the sample based on a data-driven cut-point. The algorithm stops building the tree when there are no more statistically significant associations between the dependent variable and covariates in any node (subgroup). Cases with missing values on the split variable were allocated randomly to a node. The proportion of dropouts in each subgroup was reported. The algorithm was performed in R (version 4.1.1) with the "partykit" package and the "ctree" function.

3.6.4 Paper III

The Health Directed Activity scale has not previously been validated in cancer populations. One reason for this is that the physical activity domain may not be relevant for all research questions and interventions [84]. Because of this, and as one item of the scale does not solely focus on physical activities, a confirmatory factor analysis was applied to evaluate the appropriateness of using the scale as a measure of physical activity participation. The comparative fit index and factor loadings were satisfactory; thus, the scale was used as intended with all items included. Previous validation studies have reported good construct validity across the HeiQ scales, with slightly weaker reliability of the Self-Monitoring and Insight scale [79, 80, 84].

The associations between self-management constructs and physical activity participation were assessed with multivariable linear regression models. All models were performed separately for each gynaecological tumour type, and were adjusted for the participant characteristics age, BMI, educational level, FIGO cancer stage, years from diagnosis, partner status, employment, and country. The significance and strengths of associations were reported. Covariates with a hypothesized influence of physical activity participation were adjusted for. To limit the possible impact of different recruitment strategies across countries, country was also adjusted for. As the constructs were measured on the same scale, unstandardized regression coefficients were reported representing the strength of associations. The 95% confidence intervals (CIs) for the coefficients were included as coefficients non-overlapping CIs suggest significant differences in the magnitude of associations.

3.7 Ethical considerations

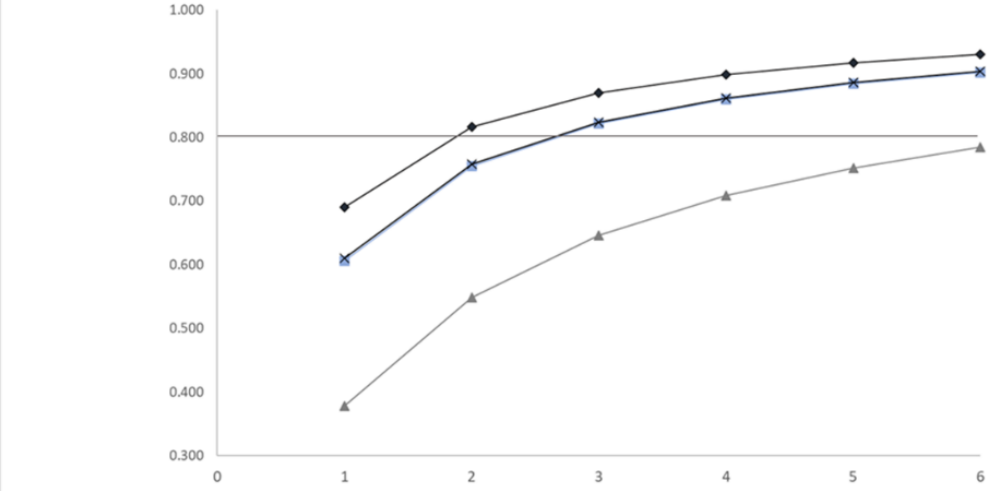
Data analysed as part of the present thesis had previously been collected from studies approved by regional ethics committees. Thus, the Research Ethics Committee of the Faculty of Health and Sport Sciences at the University of Agder considered the current PhD dissertation to not require additional ethical approval. The Phys-Can study was approved by the Regional Ethical review Board in Uppsala, Sweden (2014/249) and registered in ClinicalTrials.gov (NCT02473003, Oct 2014). The CRC-NORDIET study was approved by the Reginal Committees for Medical and Health Research Ethics, Norway (2011/836), and the data protection officials at Oslo University Hospital and Akershus University Hospital and registered in ClinicalTrial.gov (NCT01570010). To be included in the POLARIS database, studies had to be approved by regional ethic committees, obtain written informed consent from participants, and conducted in line with the declaration of Helsinki. The POLARIS study was registered in the International Prospective register of Systematic Reviews (PROSPERO: CRD42013003805). The InCHARGE study was approved by the regional committee of medical research ethics in Norway (2018/441) and the Danish Data Protection Agency (18/39742), as well as the data protection officials at the participating hospitals. In the Netherlands, the medical ethical committee declared that ethical approval was not required as the study did not fall under the Medical Research Involving Human Subjects Act (NW2018-38). All participants gave written or online informed consent. Data was anonymized prior to merging and analysis.

4 Summary and discussion of results

4.1 Paper I

The minimum monitoring period required for reliable estimates of device-based physical activity levels was two monitoring days for light intensity, and three monitoring days for moderate and moderate-to-vigorous intensity (Figure 3). Thus, a six-day continuous monitoring protocol was possible to halve, as estimates from three monitoring days appeared representative of the monitoring period based on the intra-individual variation in physical activity levels. While 75% of the sample complied with the six-day protocol, 95% had three valid monitoring days.

The level of vigorous intensity physical activity was low throughout the sample, thus, the result for MVPA reflected that of the results for moderate intensity. Furthermore, the intra-individual variation in vigorous intensity physical activity was substantial and reliable estimates were not obtained across the six days. Therefore, longer monitoring periods appear necessary for reliable estimates, or time in vigorous intensity should be included as MVPA.



Light physical activity	0.690	0.817	0.870	0.899	0.918	0.930
Moderate physical activity	0.606	0.755	0.822	0.860	0.885	0.902
Vigorous physical activity	0.378	0.549	0.646	0.709	0.752	0.785
Moderate-to-vigorous physical activity	0.610	0.758	0.824	0.862	0.887	0.904

Figure 3. The intra-class correlation coefficients from the Spearman Brown formula, representing the reliability of an increasing number of monitoring days to represent the six-day period. A cut-off of 0.8 was used for sufficient reliability.

Certain demographic and clinical characteristics of the participants were associated with different variances, thus affecting the reliability of monitoring days (Figure 4). Colorectal cancer, overweight or obese BMI, low-medium educational level, and being 60 years or older were associated with higher day-to-day variance in light physical activity, increasing the number of monitoring days for reliable estimates. Breast cancer, and overweight or obese BMI were associated with higher variance in moderate physical activity, while participants with overweight and obese BMI also exhibited higher variances in MVPA, increasing the number of required monitoring days. Breast cancer, being female, obese BMI, and age 60 years or older were associated with lower variance in vigorous physical activity, resulting in reliable estimates of time in vigorous intensity physical activity in these participants.

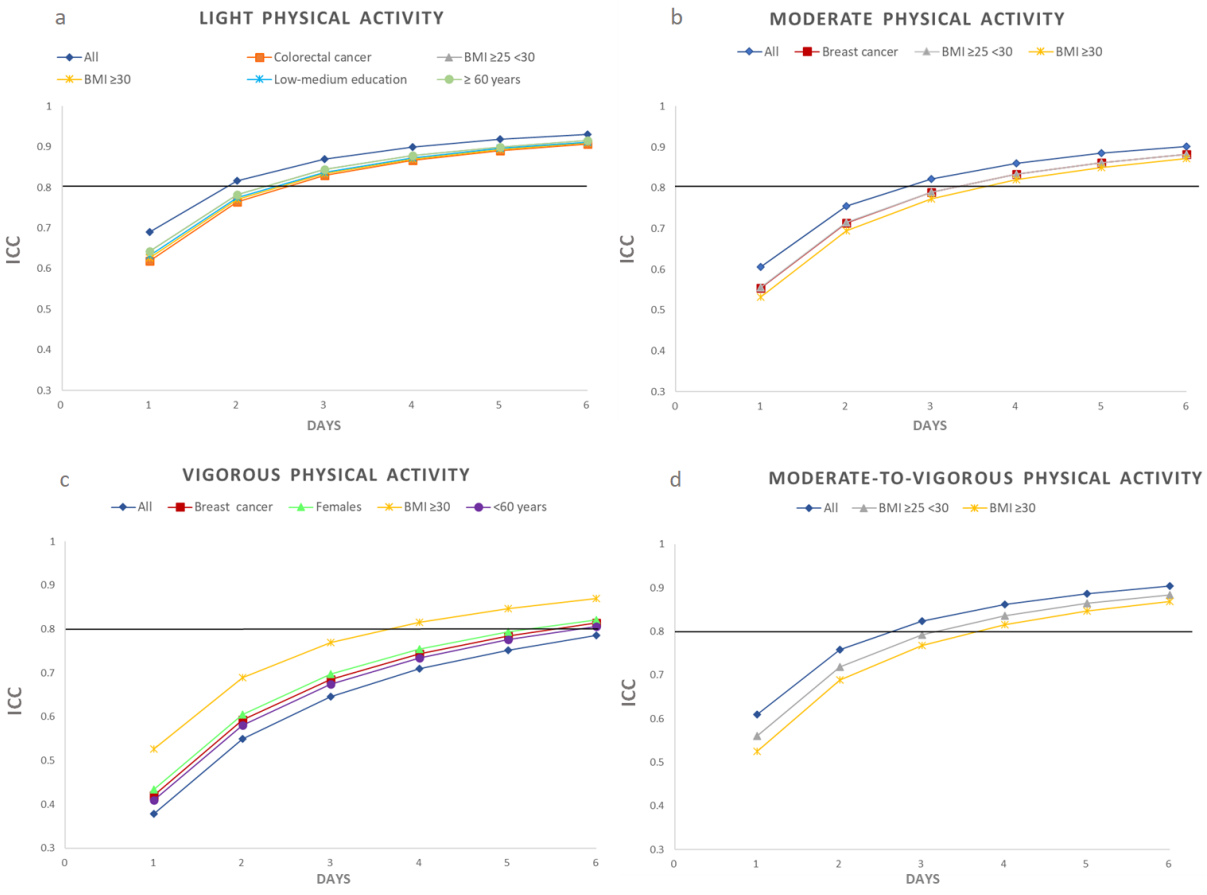


Figure 4 (a, b, c, d). The reliability (intra-class correlation coefficient) of an increasing number of monitoring days to represent the six-day period within subgroups who required a different number of monitoring days for reliable estimates. A cut-off of 0.8 was used for sufficient reliability.

These findings highlight the possibility of optimizing a physical activity monitoring protocol to both provide reliable data and be less burdensome to study participants. These results are in line with the findings from a previous study where SWAM was applied in the general population with the same daily wear-time of ≥22 hours [94]. Scheers et al., also reported that three monitoring days were necessary for obtaining an ICC >0.8 for light, moderate, and moderate-to-vigorous intensity physical activity. Similarly, reliable estimates of MVPA with three monitoring days have been found in a sample of colorectal cancer survivors with a different wearable device [95]. To the authors knowledge, there has been no previous assessments of the impact of sex, age, cancer type, weight status or education on the reliability of monitoring days in cancer survivors.

Compared to a larger amount of evidence from the general population, it appears that cancer survivors may have similar or slightly lower intra-individual variability in light and moderate intensity physical activity, but higher variability in vigorous intensity [39, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105]. This suggests differences in physical activity patterns, which appear to have implications for appropriate monitoring protocols.

As previously mentioned, in general adult populations, there is inconclusive results regarding the duration of a reliable monitoring period. It is possible that future accumulation of similar analyses across cancer populations will result in the same trends because there are several factors that affect the variability of physical activity estimates. A large proportion of the differences across studies are likely attributed to different wear-times and monitoring periods [37]. Thus, it is crucial that studies strive to identify a best practice for monitor wear and adapt comparable protocols, but most importantly, report daily wear-time and number of days included in assessments. However, other factors such as different levels of measurement error across monitors can also cause differing variability of estimates for the same physical activity level. This should be clearly reported when possible and considered when comparing results. Additionally, the contribution of bias on the total variance in physical activity estimates should always be assessed [88]. Ideally, estimates would only be affected by actual variations in physical activity levels. Only then can we truly determine reliable monitoring periods for different participants, contexts, and timeframes.

Defining the minimal required monitoring period, may facilitate study participation and completion rates through less participant burden [38, 39]. Hence, reducing dropout and improving statistical power while preserving the external validity of the initial sample. Minimizing the monitoring period is a more pragmatic approach that also considers ethical aspects of monitoring individuals possibly experiencing an additional burden from their cancer diagnosis or late-effects.

The measured physical activity levels in the total sample are presented in Table 4. Based on time in MVPA, participants seemingly exceeded the recommended 150 minutes MVPA weekly, and 91% reached this threshold based on their daily average. However, when comparing this with their relative energy expenditure as estimated by the PAL-value, participants did not appear to be sufficiently active with a mean PAL of 1.63 and only 25% achieved a PAL ≥1.75 (Figure 5). Reaching a PAL of 1.75 corresponded with having 105 minutes of MVPA daily or 735 minutes weekly.

Table 4. Mean daily minutes spent in different physical activity intensities.

Mean daily physical activity n=736							
Light intensity		Moderate intensity		Vigorous intensity		MVPA	
Mean minutes (SD)	CV%	Mean minutes (SD)	CV%	Mean minutes (SD)	CV%	Mean minutes (SD)	CV%
220.49 (81.97)	37.18	75.99 (54.19)	71.31	3.43 (7.48)	218.04	79.42 (57.29)	72.14

MVPA – moderate-to-vigorous intensity physical activity; CV – coefficient of variation; SD – standard deviation.

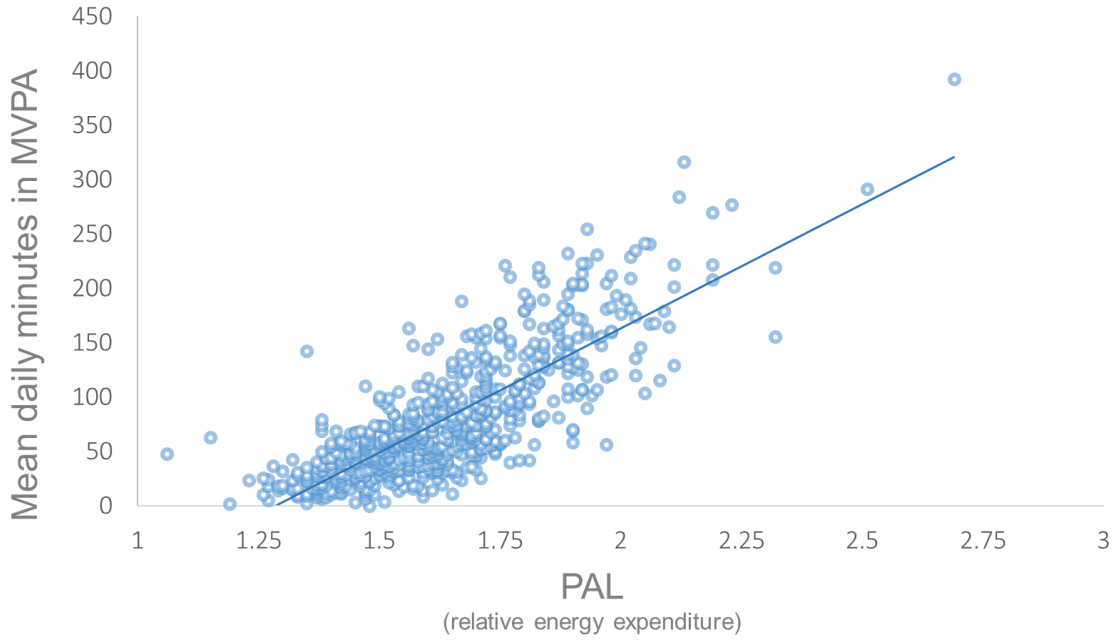


Figure 5. Comparison of minutes spent in moderate-to-vigorous intensity physical activity (MVPA) daily and PAL-values representing relative energy expenditure. The respective recommendations are reaching 150 minutes of MVPA weekly (≈ 21.4 minutes daily) and achieving a PAL of 1.75.

Similar findings have been reported in a previous study of adults, where the researchers concluded that estimates from sophisticated monitors should not be compared with the current physical activity recommendations [106]. Doing so can make people erroneously form the view that they are exceeding the recommendation by several fold if adjustments are not made. Thus, this conclusion may also be relevant for cancer populations. Thompson et al., (2016) proposed that a level of 1000 minutes MVPA weekly, corresponding with 15% of waking time, was a more appropriate target when using continuous monitoring [106]. This is slightly higher than the 735 minutes corresponding with a PAL of 1.75 in the present study. However, the possible measurement error of using a predictive equation for estimating basal metabolic rates should be considered, although the Mifflin's formula has been found most valid when compared to other equations [107, 108]. Nevertheless, it may have overestimated or underestimated basal metabolic rates that were compared with the total energy expenditures as measured by the SWAM, forming the PAL values. Furthermore,

using such equations may not be valid for use at the individual level, and further studies should be conducted using more accurate measures of basal metabolic rate [107]. These findings illustrate some of the challenges that emerge as technology advances, such as comparing modern physical activity monitoring with recommendations based on other data sources [106, 109, 110]. Scientific methodologies should be adapted to such developments, ensuring that research remains current and relevant for societal needs.

4.2 Paper II

In the pooled sample of participants from 34 different exercise RCTs, several participant and intervention characteristics were significantly associated with dropout from the intervention groups. Four significant associations with dropout were identified and their combinations resulted in five distinct subgroups. Two of these subgroups exhibited particularly high dropout rates compared to the other participants. These were cancer survivors with BMI $\geq$28.4 kg/m^2 who participated in resistance exercise interventions or unsupervised mixed exercise interventions (19.8% dropout), and the remaining cancer survivors with BMI $\geq$28.4 kg/m^2 who had low-medium education (13.5% dropout) (Figure 6).

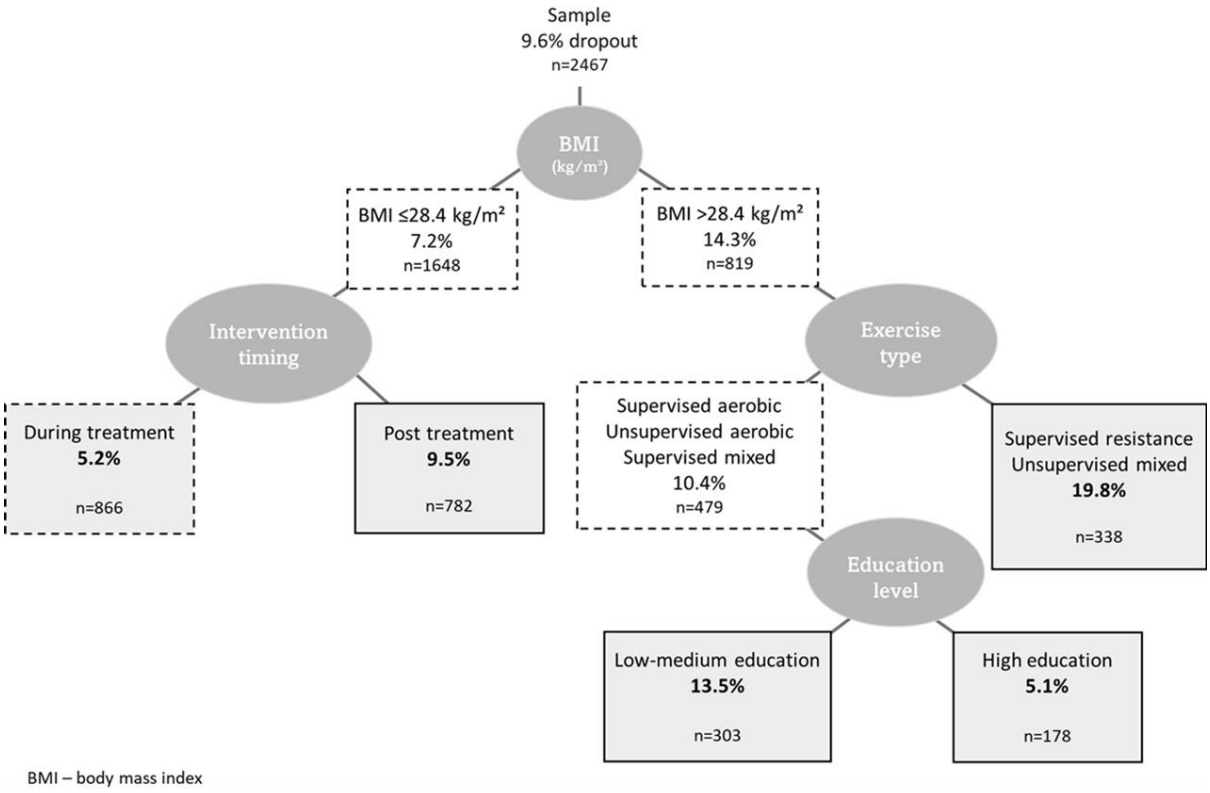


Figure 6. Conditional inference tree (Ctree) splitting the sample based on the strongest associations with dropout, resulting in five subgroups.

In line with the present findings, more cancer survivors have previously been found to drop out of resistance exercise interventions relative to aerobic exercise interventions [111, 112]. However, there is currently few RCTs employing only resistance exercise among cancer populations [111]. Interestingly, the higher drop out from resistance exercise and unsupervised mixed interventions was significant among participants with higher BMI, but not among participants with lower BMI. Future studies should assess whether higher BMI is an actual barrier for completing resistance and unsupervised mixed interventions or if other underlying explanations emerge. There appeared to be somewhat higher completement of the supervised interventions, as has been found in previous studies [111, 113]. This may be dependent on exercise type, as the supervised resistance exercise showed the highest dropout in the present study. Nevertheless, breast cancer survivors with higher BMI have previously reported preferring to exercise at a facility [114], and the present sample did not include any unsupervised resistance exercise interventions for comparison.

Higher BMI and number of co-morbidities have been associated with less physical activity and higher negative outcome expectations among breast cancer

survivors [114, 115]. Lower education has also been associated with worse outcome expectations among cancer survivors [116], as well as lower physical activity levels, lower health literacy, and lower willingness to participate in exercise programs [117, 118, 119]. In line with this, previous exercise adherence has been associated with more exercise intervention adherence among cancer survivors [120]. Likewise, the combination of both low-medium education and higher BMI were associated with more dropout in the present study, although BMI exhibited the strongest association.

Considering that the cancer survivors in the identified subgroups shared the same characteristics, the high dropout rates in two of the groups becomes more conspicuous as this dropout did not appear random but rather strongly associated with their respective characteristics. This detection of patterns is one of the strengths of employing a data-driven approach [121]. The observation raises concerns about the potential underrepresentation of these cancer survivors in the results of exercise trials, impacting the external validity and generalizability of the findings. The higher dropout may also indicate that these participants require additional or different support to complete exercise programs.

A significantly higher dropout was also observed for post-treatment interventions compared to interventions conducted during treatment. There may have been differences between these interventions in the exercise programs, provided support, or supervision beyond what we included in the present assessments. There may also be differences in motivation or outcome expectations between participants who are enrolled during treatment as opposed to after [122, 123]. However, the extent to which participants adhered to the interventions before missing post-intervention assessments was unknown.

The present study provides insights that are rarely feasible to assess within individual studies, where the sample size of dropouts may be too small for meaningful analysis. An important implication of these findings is the greater loss of participants with overweight, obesity, and lower educational levels; individuals who often present insufficient physical activity levels and stand to gain significant benefits from improved physical activity participation.

4.3 Paper III

Out of the seven self-management constructs assessed in relation to physical activity participation, two constructs showed particularly strong associations across gynaecological tumour type (Figure 7). These were the Positive and Active Engagement in Life and Self-Monitoring and Insight scales. Thus, cancer survivors reporting more physical activity participation appeared to be more actively engaged in their life, planned and prioritized activities and hobbies they found enjoyable and life-fulfilling, and were motivated to improve their life-circumstances. They also possessed self-monitoring skills, an ability to self-manage their condition by taking appropriate actions when symptoms worsened, had reasonable expectations to themselves, and had insight into their health issues and factors affecting these.

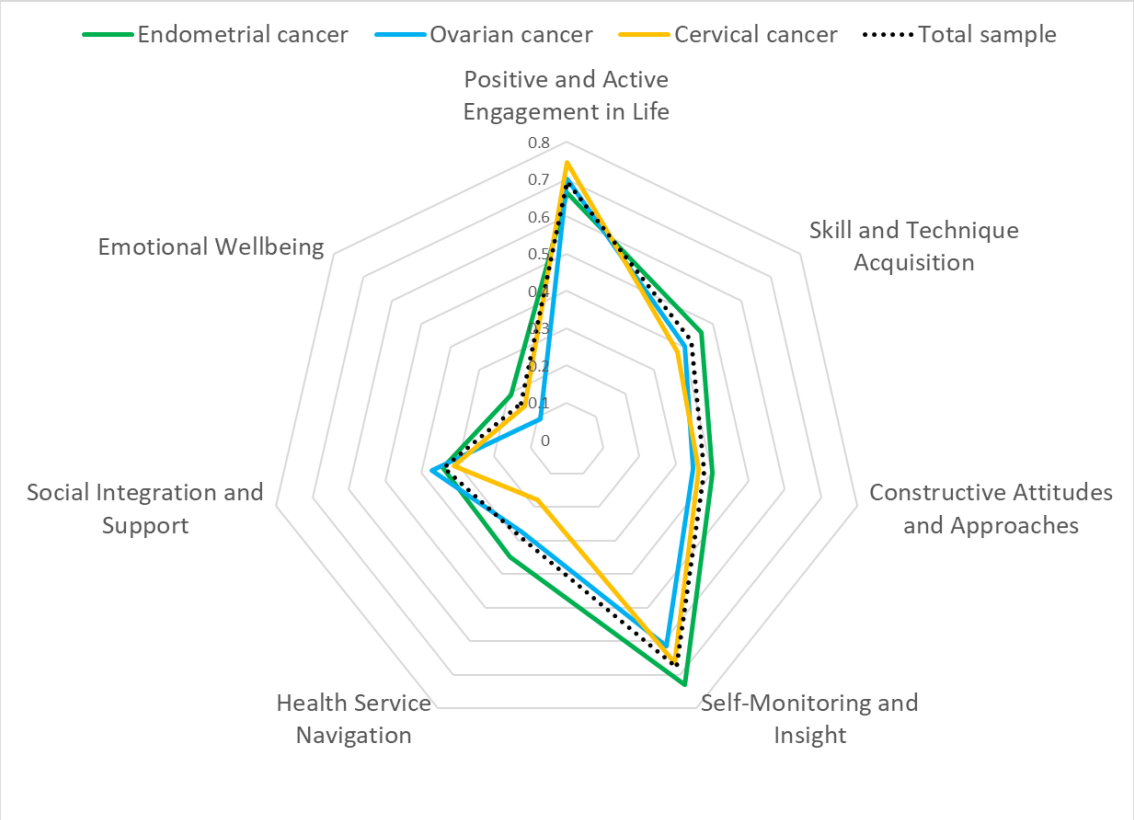


Figure 7. Radar plot of regression coefficients from the associations between self-management constructs and physical activity participation.

Among ovarian and cervical cancer survivors, the association between Positive and Active Engagement in life and physical activity participation was significantly stronger than the other scales, except the Self-Monitoring and

Insight scale. Among the endometrial cancer survivors, both the Positive and Active Engagement in life and Self-Monitoring and Insight scales showed significantly stronger associations with physical activity participation.

While no previous study has, to the author's knowledge, assessed the associations between self-management constructs and physical activity among gynaecological cancer survivors using the HeiQ, some comparable findings have been reported. Prioritization of enjoyable activities, as measured by the Positive and Active Engagement in Life scale, reflects a sense of autonomy. Patients with advanced cancer, including ovarian and cervical cancer, have reported participating in physical activities as a means of taking control of their health [124]. Exercise interventions grounded in autonomy have shown increased participation in, and maintenance of, physical activity behaviours [125, 126]. This also exemplifies intrinsically motivated behaviours, as they are performed based on joy and satisfaction, rather than external incentives or pressure [127]. Furthermore, not perceiving an exercise program as tailored to one's prerequisites have been defined as a barrier for exercise program implementation among cancer survivors [66]. Furthermore, a RCT testing an exercise intervention supporting autonomy and informed choices in a sample of women, resulted in higher physical activity levels and weight-loss compared to controls [128].

The ability to take appropriate actions in relation to one's health, as measured by the Self-Monitoring and Insight scale, reflects both a level of health literacy and self-efficacy. These concepts have been associated with positive changes in physical activity behaviour and self-efficacy, which is a central part of the self-determination theory [60, 129, 130, 131]. More physical activity participation with higher Self-Monitoring and Insight may represent extrinsic motivation, as the physical activity may not be performed for enjoyment, but to achieve improved health outcomes long term [127]. This association may specifically represent the most autonomous form of extrinsic motivation referred to as integrated regulation, where the individual recognizes and identifies with the value of the activity while also finding it congruent with other core interests and values [127]. While physical activities performed because of intrinsic motivation are based on interests and enjoyment, physical activities performed because of integrated regulation are viewed as worthwhile, even if not enjoyable [127].

Resilience, defined as a dynamic process of facing adversity related to the cancer experience, may also be reflected in the scales Positive and Active Engagement in Life, and Self-Monitoring and Insight through the ability to accepting one's condition while being motivated to improve it [132]. Among cancer patients receiving treatment, resilience has been associated with higher physical activity levels [132]. The present findings suggest that Positive and Active Engagement in Life, Self-Monitoring and Insight, and different factors related to self-efficacy, knowledge, motivation, outcome expectations, and resilience may be relevant to test in relation to physical activity behavioural change among gynaecological cancer survivors.

5 Methodological considerations

5.1 Study design

5.1.1 Reliability of monitoring protocols

When addressing the first objective, two samples wearing the same physical activity monitor, following the same monitoring protocol, were pooled. However, there may have been differences in how instructions regarding the protocol were given, which could have impacted how strictly they adhered to the wear-time criteria, and whether they altered their activity levels.

It is important to acknowledge that previous research has highlighted how the number of participants in the analysis affect reliability estimates [37]. When the number of participants increases, the number of monitoring days required for overall reliable estimates decreases, and vice versa. Thus, the reliable three-day period identified in the present analyses may be representative to the respective sample size (n=736), and we do not know whether smaller sample sizes of cancer survivors may require more monitoring days. This could have been explored with the present data by randomly excluding a varying number of participants from analyses. Yet, if the participant burden related to using wearable devices is to be reduced (regardless of resources and logistics), it would be more appropriate to increase the sample-size as opposed to monitoring days.

The variance from six days of physical activity monitoring was used as the foundation to calculate the minimum monitoring period. Thus, the reliability estimates are only representative of this time-period. This is appropriate when the respective timeframe is what we want to obtain estimates for. However, an initially longer monitoring period would have been ideal, as this would have allowed more flexibility of the calculations and could have been used to experiment with variances from different period durations. In other words, if we had employed a longer monitoring period, provided participants complied with it, we could have used the variance from a different number of days to obtain the ICC. These coefficients would represent the variance of different periods and their results from the Spearman Brown formula could be compared. For example, the minimum monitoring period representing 10, 20, and 30 days could be compared. It is possible that the minimum monitoring period increases with the number of days used to calculate the ICC, but it is also possible that the variance even out at some point (i.e., the minimum monitoring period may not increase

proportionally with the reference period). Thus, with longer initial monitoring periods it may be possible to explore and define a general standardization for a minimum monitoring period for reliable estimates. Nevertheless, activity levels assessed over time are more likely affected by other factors contributing to the variance. This could be the change of seasons, varying weather, and vacations, or other factor more difficult to measure such as changes in lifestyle. In cancer populations, cancer related factors such as the coming and going of late-effects may also be factors to account for. With the shorter timeframe applied in the present study, such factors did likely account for little of the variance compared to a longer timeframe. However, these areas are largely unexplored as few studies have made such assessments, with currently no such evidence from cancer populations. There is also a possible issue with adoption of the monitors and protocol compliance, with long monitoring periods possibly causing increasing attrition and a biased sample [35].

With continuous monitoring, the number of daily measurement hours can also be varied in the calculations. This can be used to define the threshold for how many hours the monitor should be worn during the day to reliably represent the respective day. As this calculation would be based on the hour-to-hour variance in physical activity, such calculation may require averaging of results from different days to find an overall representative threshold. Information about waking time, sleep, and time of day should then be accounted for or separated in the analysis, as removing two hours during the night as opposed to during the day will likely affect the measured activity level differently. Previous assessments have suggested that the accuracy of physical activity estimates increases with more daily measurement hours [133, 134]. Some assessments have been conducted among healthy populations, while others have tested clinical populations including diabetes type 2 and stroke patients [133, 134, 135, 136]. However continuous monitoring is rarely used, and, to the authors knowledge, no such assessments have been performed in cancer populations. However, with the rise of modern wearable devices, assessments including continuous wear are relevant to perform. This research could further inform appropriate monitoring protocols, as the 22 hours criteria in the present study was based on previously applied protocols and not reliability analyses [94].

5.1.2 Assessing dropout across numerous exercise trials

When addressing the second objective, dropout from the intervention groups of 34 trials was assessed. However, the control groups should ideally also be included in dropout analyses. If the control groups are biased by data missing not at random, it will compromise comparisons with the intervention group. The findings among control groups may require different interpretations, as they are not performing a given intervention, and such assessments warrant further investigation. If we had included controls in our assessments, with the intervention characteristics of the trial they participated in, we could have obtained more insight into the underlying factors leading to dropout. If, for example, resistance exercise interventions were also associated with dropout in the control groups, it would suggest that a latent variable related to these interventions caused the associations and not the exercise. In the present study, the only intervention characteristic directly relevant to controls was the intervention duration, as it is tied to the study as a whole and not just the exercise program. To strengthen the assumption that intervention characteristics directly impacted dropout, we would ideally not have any significant associations between these characteristics and dropout among controls.

Information about when during the study period participants dropped out should have been included in the current analyses, but this information was not available. This information would not change the overall observed associations with dropout but could have provided more information about those dropping out. By accounting for this, and possibly also adherence, we could have assessed whether some are more likely to drop out early or later in the intervention period, which could further inform feasibility. Previous assessments of the Phys-Can study found that more than 50% of the dropouts did so during the introduction phase (first four weeks) of the study [32]. Since this information was not accounted for in the POLARIS study, it is possible that some completers and dropouts had the same level of intervention adherence, differing only in the completion of post-intervention measures. Consequently, the current evidence is not sufficient to draw conclusions about exercise intervention feasibility across different cancer survivors. Nevertheless, the study indicates that certain variables characterize participants without complete data, causing data missing not at random.

5.1.3 Association between physical activity and self-management

With the cross-sectional design of the InCHARGE study, behavioural change effects from the self-management constructs on physical activity participation cannot be determined. Longitudinal and experimental studies aiming to increase physical activity levels through the respective self-management constructs would be required to explore causal relationships. Nonetheless, the current findings can serve as valuable insights for the development of interventions for further testing. Given the multitude of self-management skills possible to target in interventions, relevant constructs for physical activity behaviour are imperative to explore.

The call for implementation of self-management support in the cancer care necessitates more pragmatic studies. However, it may be necessary to first explore what such self-management support should contain, and which effects can be derived through research placed towards the explanatory end of the continuum [8]. If meaningful effects are observed, the subsequent step would be to develop interventions with broad applicability suitable for implementation. However, to which degree self-management support should be tested exploratory in highly controlled settings are questionable, as it may lack representativeness of real-world settings. Careful planning and involvement of different stakeholders, deliverers, and receivers should be included. Real-life contextual factors may contribute to how self-management support in perceived (e.g., different preexisting factors within individuals, Figure 2) and adopted (e.g., environmental factors such as resources).

Previous research has shown how intervention receivers' beliefs impact the adoption of exercise programs [125, 137, 138]. The placebo effect of believing that one is receiving an individualized or optimized exercise program has been found to increase both motivation, performance, and adherence to the program, further impacting exercise outcomes [125, 137, 138]. From a self-management or behavioural change perspective, these placebo effects or impacts of context may be desirable rather than avoidable, which is in high contrast to the goal of exploratory studies.

5.2 Measures and data handling

5.2.1 Estimating physical activity levels

To conduct the reliability analyses in Paper I, we applied a sophisticated monitor with a modern protocol relevant to the increasing use of continuous physical

activity monitoring. The SWAM has temperature sensors and an accelerometer. Based on raw data from these sensors, an algorithm created by the manufacturer estimates energy expenditures that are further used to estimate physical activity levels through metabolic equivalents. How the algorithm performs these calculations are not know to researchers applying it and remains a “black box”. In validation studies, the algorithm appear to perform satisfactorily, both for the original SenseWear and the Mini version, but fewer studies have validated the Mini [72, 73, 139, 140, 141, 142, 143, 144, 145]. Nevertheless, the devices have performed suboptimal for activities at higher intensities which could be the reason for less reliable estimates found for vigorous intensity physical activity [72, 139, 143, 144]. Inaccuracy in estimations could increase the measurement error of vigorous physical activity and thus extending the monitoring period required for reliable estimates.

In populations without cancer, several studies have explored the reliability of monitoring periods based on variances in physical activity estimates [39, 94, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105]. These studies, however, apply widely different timeframes, both hours of wear-time and number of monitoring days. Not unexpectedly, the timeframes identified as reliable differs accordingly and range from 2 to 10 days. The difference in daily wear-time is likely a contributor to these variations as it may impact the variability in measured activity levels. Also, the number of individuals assessed in the analyses vary greatly from 50 to several thousand, likely affecting the standard error as previously described [37]. With the increased use of sophisticated wearable devices, both by consumers and in research, it is highly relevant to consider continuous monitoring protocols as these devices are, almost without exception, designed to be worn continuously.

Future studies should explore how different physical activity patterns impact the variability in activity levels. Whether an individual engage in exercise or not, may impact the variability in physical activity. Exercise during some days, with sedentary time other days, may increase the day-to-day variation. On the other hand, it is possible that non-exercisers have a more unpredictable activity pattern with more spontaneous physical activity creating larger variability. Such assessments could yield implications for determining whether monitoring periods should differ based on activity patterns.

When estimating physical activity levels through wearable devices it is often possible to specify through the software whether activity must be in bouts (e.g.,

be performed in durations of at least 10 minutes) to be counted. Using the 10 minutes bout-requirement was common practice until the World Health Organization 2020 *Global Guidelines of Physical Activity and Sedentary Behaviours* removed this criterion and stated that all physical activity matters despite duration, changing how physical activity levels are estimated [146]. In line with these guidelines, the present study did not include a criterion for bouts. Despite the change in the guidelines, the recommendation of 150 minutes MVPA weekly still stands. This may be the reason for the high activity levels observed in the present sample where most exceeded the physical activity recommendations. Additionally, the development of the recommendations were mostly based on measures collected using other methods and not objective continuous monitoring [147]. The relative energy expenditures expressed as PAL values suggested mostly insufficient activity levels. Similar findings have been found in previous research with comparable measurement protocols in other populations [106]. However, we cannot rule out that participants changed their activity levels as a result of being monitored, or that using a predictive equation for estimating basal metabolic rate was not sufficiently accurate. Nevertheless, the current reliability analyses were concerned with the variance estimates and not the time spent in physical activity.

It should be noted that the SenseWear Armbands are no longer in production. As a result, further validation studies are unlikely to be conducted. Researchers currently utilizing other devices in cancer populations should conduct similar reliability analyses to compared results. This approach can enhance the standardization of physical activity monitoring among cancer survivors and improve comparability across studies.

5.2.2 Utilizing individual patient data across trials

Individual patient data meta-analysis refers to the use of information available at the patient-level rather than relying on study-level data when comparing result across different studies. The use of individual patient data has been found more precise in detecting differential effects compared to assessments with summary statistics [148]. Summary statistics from a great number of trials are typically required to achieve similar results as individual patient data that contains the heterogeneity of the samples and better statistical power [148].

On the other hand, it is possible that harmonization of data from different studies simplifies or loses some information. This can happen when variables measured

at different scales, or divided into different categories, are collapsed across trials. In the present study, although trials were categorized based on the same type of exercise, there were still differences in the prescribed exercise. For example, some unsupervised aerobic interventions could be walking-based while other could be indoor activities. Furthermore, it is possible that some dropouts were excluded prior to data sharing and harmonization, as per protocol analyses excluding dropouts is common practice among RCTs despite the impact on external validity [4]. Some cancer survivors agreeing to participation could also have dropped out before baseline assessments, however, these participants are usually not randomized until after baseline, and are thus not classified as intervention participants. Nevertheless, information about these participants would also contribute to a better understanding of dropout.

The use of individual patient data may have diluted some selection bias present within original trials. The associations with dropout were consistently found across trials with similar characteristics which strengthens the findings. For example, the subsample with the highest dropout in the present study (high BMI participating in resistance and unsupervised mixed interventions), contained participants from 13 different trials, which strengthens the conclusion that the characteristics of this subgroup, or something related to these, impacted dropout.

Certain cancer specific variables related to health status may impact whether cancer survivors are likely to complete exercise trials. However, data from the POLARIS database was already harmonized upon acquisition, which limited the possibilities of including information about cancer stage and cancer treatment in the analyses because of insufficient harmonization. Hence, future studies should continue the use of individual patient data, but should ideally also include control groups, dropout before randomization, measures of adherence, and time point at dropout.

5.2.3 Self-reported physical activity participation and self-management

In the InCHARGE study, variations in recruitment and data collection methods were present across the three countries. In the Netherlands, eligible cancer survivors were identified through the cancer registry. In Norway, responsible doctors identified potential participants, while in Denmark, an electronic system was used. These differences may have impacted the selection of potential participants approached. Recruitment through an electronic system may not reach the oldest individuals or those with poor digital skills who do not use this system

or have difficulty doing so. On the other hand, the use of this electronic system resulted in a much higher response rate in Denmark compared to the strategies used in the Netherlands and Norway. In Norway, the selection performed by the physicians may also result in selection bias. Information about age, height, weight, education, partner status, and employment were self-reported. Thus, the accuracy of this information cannot be established and are at risk of self-report bias.

The HeiQ is a validated and extensively tested instrument with broad applicability [80]. Comprising eight scales that assess independent dimensions of self-management, the questionnaire underwent a meticulous development process with significant stakeholder involvement to ensure practical relevance [79]. However, it is crucial to recognize that the present findings are confined to the content of these dimensions, although they are related to other aspects of self-management and behavioural change. Nevertheless, such related concepts have also shown associations with physical activity [60, 125, 126, 128, 131, 132].

In a comprehensive review evaluating questionnaires measuring empowerment in cancer populations, the HeiQ was found to be the best performing questionnaire, receiving positive scores for content validity, internal consistency, construct validity and floor and ceiling effects [149]. The HeiQ was identified as the sole questionnaire applied in cancer populations that captured all four components of empowerment, as defined in the review. However, the HeiQ scales measuring empowerment, included in the study by Eskildsen et al. (2017) were based on the validation study conducted by Maunsell et al., (2014) [84]. Hence, the scales Health Directed Activity, Positive and Active Engagement in Life, and Self-monitoring and Insight were not part of this definition of empowerment [84].

The HeiQ scales were originally measured on a 6-point scale but were simplified to a 4-point scale during the questionnaire construction due to respondents struggling to differentiate between the midpoints “slightly agree” and “slightly disagree” [150]. During development and validation, the Self-Monitoring and Insight scale showed the lowest reliability, which should be considered when interpreting the findings. If the items comprising this scale measures slightly different concepts, we do not know which content was most strongly associated with physical activity.

In the present study, the measure of physical activity participation was self-reported. As previously mentioned, objective monitoring has been found more accurate for estimating time in physical activity compared to self-report methods [34]. However, the purpose of the scale was not to measure time spent in different intensities. To achieve increased physical activity levels through self-management support, the individual must take responsibility for their physical activity behaviour. Consequently, measuring the intention to participate in physical activities to improve one's health was of interest rather than having specific values for time in different intensities. Furthermore, the participants were spread out geographically, also within their respective country, which complicated the use of wearable monitors. However, future studies assessing the behavioural change effect of the self-management constructs should also include objective measures to quantify changes in activity levels.

5.3 Samples

The two samples pooled for analysis in Paper I consisted of breast, colorectal, and prostate cancer survivors. There was an almost equal distribution of breast and colorectal cancer survivors (42 vs 48%, respectively) with few prostate cancer cases (≈9%), and the sample consisted of mostly females (≈64%). Globally, colorectal cancer constitutes a similar proportion of new cases across males and females [6]. Approximately 45% of the colorectal cancer survivors in the present sample were females. The present results represented mostly the variability in activity levels among breast and colorectal cancer survivors, and to a smaller degree prostate cancer survivors. The majority of participants completed the measurements during treatment, but most of the colorectal cancer survivors were post-treatment, potentially contributing to the observed differences in physical activity variability across cancer types.

One comparable study has been previously conducted, and included colorectal cancer survivors >6 years post-surgery [95]. This study assessed only time in MVPA, but found the same results as the present study, i.e., that three monitoring days yielded reliable estimates. The BMI of the sample by Skender et al., (2015) and the present sample were similarly around 26 kg/m^2, but Skender et al., did not perform stratified analysis [95]. As we observed higher intra-individual variance in MVPA among participants with overweight and obese BMIs, further

studies should assess variances in samples with overweight or obesity to determine the impact on the reliability.

The average age of the present sample was similar to the median age of 66 years observed at diagnosis across cancer sites [151]. More than half of the sample had college or university level education, which may not be representative of cancer survivors with lower socioeconomic status often associated with poorer health [152]. The variables cancer stage and treatment were not assessed but should be further studied in relation to intra-individual variability in physical activity.

The POLARIS sample was on average younger (≈55 years) than the median age at diagnosis across cancer sites (66 years) [151]. The sample was mostly comprised of breast cancer survivors (71%) which is typical to the literature on exercise trials among cancer survivors which most often include breast, colorectal, and prostate cancer survivors [153]. Subsequently, the present sample had a high proportion of female participants. The second most represented cancer type was male genitourinary, constituting only 13% of the sample, while other common cancers like lung, skin, stomach, and liver cancers were scarcely represented, thereby limiting the generalizability of the findings to other cancer types. In other words, the observed associations with dropout implying impaired external validity of the exercise trials, are mostly applicable to samples of breast cancer survivors. Furthermore, the representation of underweight participants was minimal, while cancer stage was insufficiently reported, thus, frail participants were likely underrepresented in this sample. Previous research has documented how frail cancer survivors may have distinct preferences, experiences, and challenges impacting appropriate exercise programs, while also presenting lower activity levels [154, 155]. Hence, while poorer health and greater disease severity are likely associated with dropout from exercise trials, the present data did not contain information to explore this.

The InCHARGE study included only gynaecological cancer survivors. In 2020, cancers of the uterus, ovaries, and cervix collectively constituted approximately 6.9% of all new cancer cases globally [6]. However, the representation of gynaecological cancer survivors in the literature on physical activity and cancer is relatively limited compared to other types such as breast cancer [153]. This disparity may be attributed to the larger evidence base of breast cancer survivors, making them easier to target, while the safety of conducting exercise programs in this population has been established [41, 153]. Although both female breast

cancer and gynaecological cancer affects only women, the results from physical activity trials among breast cancer survivors may not be directly applicable to gynaecological cancer populations. For example, endometrial cancer survivors more often present lifestyle related comorbidities, higher BMI, and metabolic syndrome compared to survivors of other cancer types [156, 157]. While the InCHARGE sample, on average, exhibited a comparable BMI to that of Paper I and II, the endometrial cancer survivors demonstrated significantly higher BMI compared to the ovarian and cervical cancer survivors within the study. Additionally, the prognosis for gynaecological cancers can be worse with higher mortality, especially among ovarian cancer survivors and cervical cancer survivors in low-income countries [6, 152].

5.4 Statistical analyses

The first objective of the present thesis was explored using the ICC one-way random. Before deciding on this ICC model, we tested to which degree there was unexplained variance in the data. This was done by assessing bias contribution to variance together with intra-individual and inter-individual bias contribution, through comparison of results from the one-way random, two-way random absolute agreement, and two-way random consistency as recommended [88]. The bias contribution to variance was negligible, and very similar variance estimates and coefficients were found across the ICC models, thus the most parsimonious model was applied.

The appropriate choice of an ICC threshold depends on the research question and nature of the data. ICCs between 0.75 and 0.90 have been described as good reliability [87]. In validation studies where measurement tools are compared or when fluctuations in a variable should be minimal, a very high ICC is desirable, and thresholds may be greater than 0.8. As we measured physical activity in minutes, some day-to-day variations are expected and small differences in minutes do not have meaningful implications, although differences in minutes of accumulated activity may grow more meaningful as intensity increases. Considering methods applied in similar studies using physical activity data, a threshold of 0.80 was used in the present analysis [102, 103, 158]. However, some limitations are introduced when applying cut-offs. For example, the increase in ICC for moderate intensity from 0.755 when using two days to 0.822

when using three days may not have practical implications. Using two monitoring days may be as appropriate as using three. By providing the ICC values for an increasing number of monitoring days, the coefficients can be interpreted if other cut-off are of interest. For each intensity, the ICC models were also performed across subgroups of participants to assess whether such contextual factors affected the variability and reliability.

Future studies with long monitoring protocols should perform variance calculations if the number of participants not complying with the full protocol is great. Exclusion of these participants may be avoided if variance estimates of those complying to the protocol suggest that fewer monitoring days is equally reliable to use. However, assessments of characteristics differing between compliers and non-compliers should be performed as it is possible that different factors impact the variability in physical activity. If differences are observed, it may not be appropriate to generalise the reliability estimates based on the physical activity levels of the compliers, to the non-compliers. Alternatively, the variability in activity levels for a measured period among the non-compliers could be compared with the same period for the compliers, to give some indications of variance differences.

When addressing the second objective, effect-sizes were reported for the differences in characteristics between dropouts and completers in the POLARIS study. While a p-value can inform the reader about the statistical significances of differences, the effect-size represents the magnitude of the difference between groups [159]. With large samples such as this, a statistical test may demonstrate a significant difference although small, and hold no practical implications [159]. The measure of effect-size, on the other hand, is independent of sample size and can represent the practical implications of the differences, while also enabling standardized comparisons across studies.

The large sample size in the POLARIS database allowed for subgroup comparisons, providing further insight into the associations with dropout. The decision tree model was employed to illustrate these associations in an interpretable manner, revealing associations at different levels of the sample, thus, offering a more nuanced understanding of associations within specific subgroups. This approach goes beyond traditional regression models, which would typically correspond with the first step of the tree. While moderator assessments could be an option to display interactions in the data, testing all

possible combinations of variables, at different levels based on the strongest associations, is less feasible. The Ctree algorithm, on the other hand, perform these assessments simultaneously and within subgroups based on the strongest associations, and stops when no more significant associations are present. One limitation with this method is that the tree, built on the strongest associations, does not display all significant relationships. Furthermore, all variables are split into binary groups, which means that the algorithm specifies a cut-off for continuous variables and collapses groups for categorical variables with more than two categories.

The criterium for building the tree was based on a significance level, which differ from the more commonly used classification and regression tree (CART). The CART splits a sample into subgroups based on the variable creating the most separation in the outcome (i.e., the most homogeneous groups), also referred to as purity. While the CART often requires post hoc pruning or pre-specific criteria such as subgroup size, to result in a meaningful tree, the Ctree is typically more conservative and results in a smaller tree [121]. The two methods may result in some of the same splits, as the most significant associations could also create the most separation in the outcome, however, slightly different interpretations would be required. With regard to the purpose of the present study, focusing on statistical inference rather than prediction, aligns with the advantages offered by the Ctree algorithm for identifying meaningful subgroups and associations with dropout. If the purpose of this study had been to predict dropout and develop a model that could be used for prediction in new samples, the CART, a random forest algorithm, or a model with more flexibility would have been more appropriate. Statistical inference would in that case be of less interest [121]. Common criterion for pruning the CART is having leaf nodes (final subgroups) with sample sizes no smaller than 10% of the initial sample size. This criterion is often applied to the CART to limit overfitting of the tree. If this criterion were applied to the present sample, it would mean no more than 247 participants in the final subgroups. With the Ctree, one subgroup (high-education) had a sample size <247 participants, however, the larger low-medium education subgroup was also split from the parent node. Thus, the split was considered meaningful.

To address the third objective, a confirmatory factor analysis was performed for the Health Directed Activity scale although the sample of the InCHARGE study was not selected for a validation study. Therefore, the results from this analysis

should not be interpreted as the reliability of the scale. The rationale for testing the factor structure of the scale was initiated by one of the items suggesting relaxation as an example of a health-improving activity, potentially influencing the measurement of physical activity. Because of the even factor structure observed, as have been found in validation studies, the full scale was used [79, 83].

Providing a thorough description of contextual factors related to the study and the sample enhances interpretations of external validity. The effect-sizes for the differences in characteristics across gynaecological tumour types were reported, as they can differ in various characteristics including age at diagnosis, stage at diagnosis, and treatment type received [160]. The regression model was also performed separately for the tumour types and adjusted for relevant covariates. The absence of cancer treatment as a covariate creates uncertainty about the generalizability of the findings across individuals undergoing different treatments or whether some treatment types were overrepresented. Nevertheless, treatments for gynaecological cancers are highly correlated with tumour type.

5.5 Scientific theoretical perspective

While the present work mainly adopted a positivistic approach to address the three objectives, other orientations within scientific research are likely required to address tailored exercise programs, appropriate self-management support, behavioural change, and implementation of physical activity as part of the cancer care. The positivistic approach assumes that there is an objective reality that can be studied using empirical, observable, and measurable methods [161]. Such approaches often involve quantitative methods and seek to discover general laws. While contextual factors were accounted for by adjusting the statistical models in the present studies, they were still seen as objective concepts which impact the outcomes in ways that can be quantified. However, the concept of disease management acknowledge that reality is subjective and shaped by individuals' experiences and interpretations [57]. This could be represented with an epistemic perspective or research grounded in constructivism. These perspectives emphasise that learning and a change in behaviour is based on the individual's beliefs and current knowledge [162, 163], and the importance of context, often explored through qualitative methods investigating subjective meanings and

interpretations. Such methods could add to the understanding of health behaviour adoption and the development and delivery of tailored exercise programs [164]. Thus, further research aiming to translate current evidence on physical activity into broader application and impact for cancer populations should also include qualitative assessments. Qualitative methods could both be a means to include receivers, deliverers, and different stakeholders and policy makers before implementation, as well as a means to improve feasibility of exercise programs.

The importance of context, qualitative assessments, and the inclusion of decision makers, is also represented within pragmatism. Pragmatism, assessing outcomes and solutions relevant for practice settings through both qualitative and quantitative methods, may be utilised to address research questions in a practical manner [165]. This may uncover factors that might impact intervention effects outside of efficacy trials. However, pragmatic trials may not be sufficient to inform implementation studies and does not necessarily imply wide application, despite perhaps better application compared to efficacy trials [165]. It may be necessary to employ a network of planned and adaptive contributions, tailored to local circumstances to achieve applicability, and through the process of testing, refining, retesting, and re-refining theories. Lastly, research based on critical theory, examining power structures, inequalities, and issues regarding social justice, are also relevant in terms of health equity [166]. With this approach, rooted in social science, it may be possible to gain knowledge of the factors influencing the development of cancer, accessibility, delivery, and receptivity of cancer care, disease management, health behaviours, and survival in a broader context.

5.6 Ethical considerations

One critical dimension related to the underlying factors of socioeconomic status was not accounted for in the research of the current thesis. This dimension encompasses the impact of socioeconomic status on health and wellbeing and the structural actions required to ensure equitable support to all cancer survivors. Socioeconomic conditions reflect the broader context where research is translated into practice. In countries with available high-quality data, mainly high and middle-income countries, there is clear evidence of a socioeconomic gradient in overall cancer mortality and survival, with striking differences observed between the lowest and highest socioeconomic groups [152]. These inequalities affect all

stages of the cancer continuum, from prevention to end-of-life care. In low-income countries, data are often non-existent or of poor quality [152]. When available, it reveals poor cancer outcomes, often with dramatically low cancer survival even for preventable or curable cancers (e.g., cervical and childhood cancers). Low-income countries are also often facing a double burden with both the rise of non-communicable diseases and the persistence of infectious diseases. These are the consequences of limited or complete absence of crucial resources and infrastructures. Paradoxically, even in the wealthiest countries, vulnerable populations (e.g., those living in poverty and indigenous and racial minorities) experience worse cancer outcomes [152].

Thus, it is essential that self-management support, including physical activity facilitation, is framed from an equity lens. Furthermore, the delivery of self-management support is likely dependent on, and should be tailored to, socioeconomic determinants, cultural differences, geographic location, and environment [8]. This could for example be accomplished by exploring how exercise programs can be tailored to the different needs of cancer survivors with different sociodemographic, cultural, and ethnic backgrounds. There may also be large differences in how support should be provided in terms of these factors, but with the limited amount of research conducted on implementation of exercise in the cancer care, the evidence base for addressing this is scarce. The research in the present thesis did not comprehensively address these points. While educational levels were considered in the analyses, it provides limited information about the complex concept of socioeconomic status. Furthermore, ethnicity, and racial and cultural minorities were not accounted for. The data analysed in the three studies originated from high-income countries in Europe and North America, as well as Australia and New Zealand, not representing middle-to-low income countries' conditions and prerequisites.

While socioeconomic differences may not be changeable in a self-management support setting or through more physical activity participation, these are factors it is possible to target and account for to ensure that support are equally available and applicable. From a public health perspective, this necessitates innovative strategies, political commitment, and public policies. As cancer and other non-communicable disease are now the leading causes of poor health and death in many countries, health in general cannot be seen as a matter of only providing hospitals with medicines or training health-care workers. Preventing exposer to

cancer risk factors, including physical inactivity, and providing universal health coverage have been highlighted as imperative [167]. The goal should be to ensure that all people can access needed preventive and curative health-care services, including support during cancer survivorship, without falling into poverty. In this matter, scientists have a responsibility to provide evidence aimed at tackling these challenges, developing interventions that are implementable and accessible to all cancer survivors, and to focus research on vulnerable groups. This research should include the societal and economic benefits of interventions, as current evidence illustrating the numerous benefits of physical activity on the individual level has not consistently influenced decision-makers and policy development.

Another ethical consideration for the present research was the inclusion of secondary data and analyses. The objectives of the present thesis were not related to the primary outcome of the included studies. If the current data was collected specifically for the current objectives, there could have been a more optimal collection of relevant variables, such as cancer stage and treatment. We could also have tested a longer monitoring protocol when addressing the first objective, and could have used complimentary assessments of physical activity, such as objective monitoring when addressing objective three, to verify physical activity participation. Furthermore, the already harmonized data in the POLARIS database limited the impact on categorization and inclusion of relevant variables, as well as how included studies treated dropout before data-sharing. Nevertheless, a large amount of resources, as well as time and effort spent by the participants, goes into studies to generate reliable and valid scientific data. Hence, utilizing this information to inform different research questions when appropriate, is important. This is also reflected in the growing demand for open science and data sharing, which can facilitate such purposes.

5.7 Perspectives

In the current thesis, methodological considerations related to populations, measurement tools, outcomes, and methods in research monitoring and promoting physical activity in cancer populations were explored. In the population domain, the external validity and generalizability of explanatory trials were addressed. Significantly higher dropout, thus less complete data, was found

in some subgroups (Figure 8, a). These distinct, and potentially underrepresented, subgroups may require additional support or tailored programs to complete interventions. This finding may further inform where to explore targeted methods, barriers, and facilitators (b). In the domain of measurement tools, the reliability of a commonly applied physical activity monitoring period was evaluated. Reliable physical activity estimates were found for a shorter, more applicable, less resource demanding, and potentially less burdensome monitoring period (c). These finding may further be used to improve adherence, external validity, and statistical power in studies monitoring physical activity. This domain overlapped with the population domain as the impact of different participant characteristics on the "optimized" monitoring period was accounted for (d). In the outcome domain, self-management skills that may be relevant targets for facilitating physical activity behaviour change were identified (e). While further research is required to establish the behavioural impact of these skills, the targets may inform future interventions in the preparation phase further aiming for implementation. Exploring the behavioural change effect of increasing these skills, implies they are both he method and outcome of interest (f). As part of the preparation phase, the current thesis contributes with evidence for bridging the gap between exploration and implementation of integrating physical activity in the cancer care and follow-up (g).

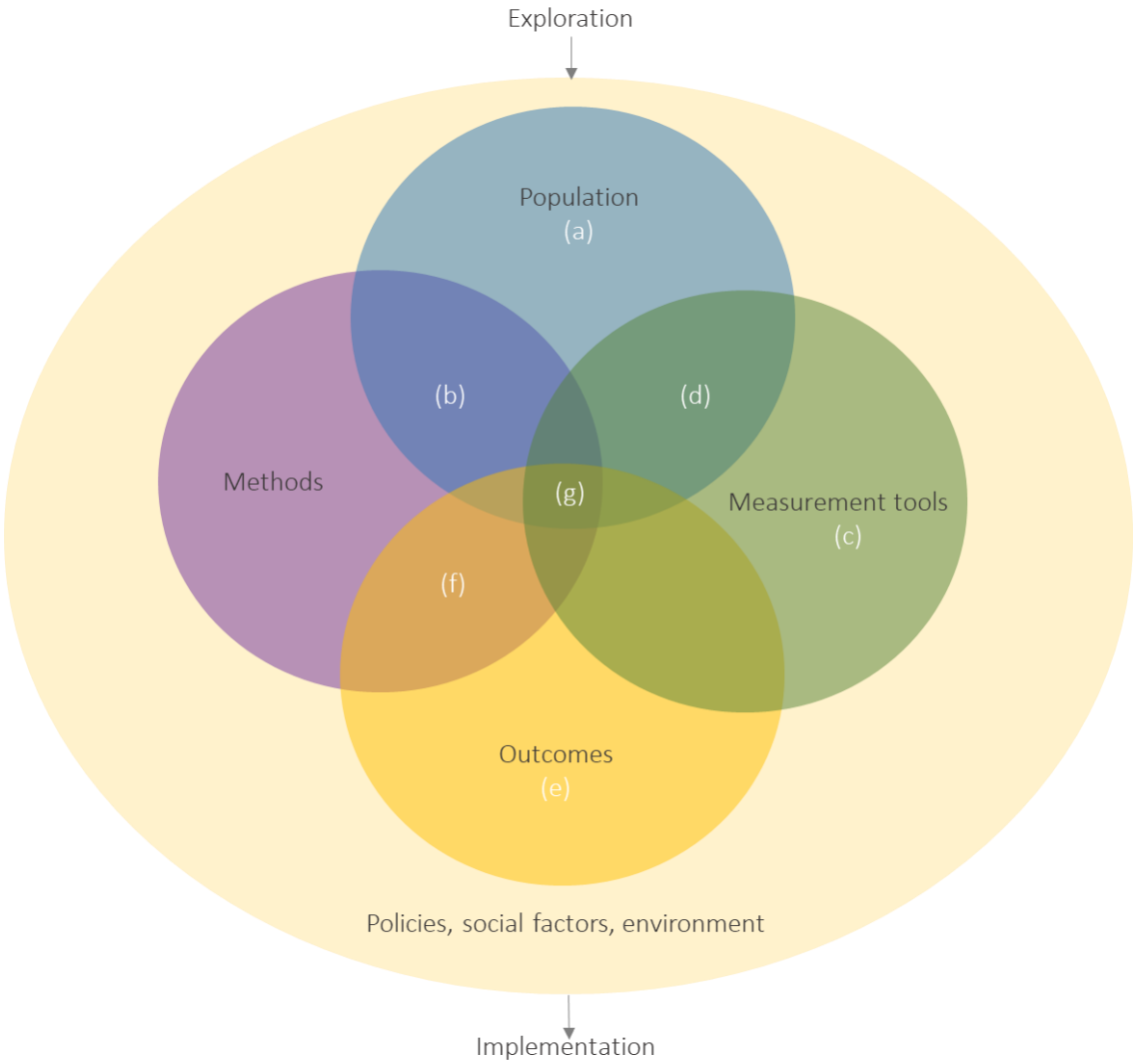


Figure 8. The evidence of the current thesis was related to the preparation phase situated between exploration and implementation. Methodological considerations related to populations, measurement tool, outcomes, and methods were addressed. To reach the next step, implementation, policies, social and environmental factors must be accounted for, but were not included in the present research.

6 Conclusion

The overarching aim of the research conducted as part of the present thesis was to close research gaps related to methodological components of studies measuring and promoting physical activity and exercise in cancer populations.

The first objective was to obtain the minimum monitoring period required for reliable estimates of device-based physical activity levels among cancer survivors. It was found that the six-day continuous physical activity monitoring protocol could be shortened to two days for light intensity, and three days for moderate intensity, and moderate-to-vigorous intensity while still obtaining relatable estimates. Reliable estimates of vigorous intensity physical activity were not obtained across the six days. These findings highlighted how it is possible to limit the participant burden in studies employing wearable devices, possibly achieving more participation, protocol adherences, and retention of participant.

Within the harmonized sample of cancer survivors participating in 34 different randomized controlled exercise trials, participants with BMI >28.4 kg/m^2 who either participated in resistance or unsupervised mixed exercise trials or had low-medium education and performed aerobic or supervised mixed exercise, were most likely to drop out. These subgroups showed 19.8% and 13.5% dropout, respectively, as opposed to the overall 9.6% dropout in the total sample. These findings suggest that certain cancer survivors are significantly more likely to drop out of exercise trials, resulting in data missing not at random.

The third objective was to assess self-management skills associated with physical activity participation among gynaecological cancer survivors. The self-management dimensions Positive and Active Engagement in Life, and Self-Monitoring and Insight were strongly associated with physical activity participation. The skills comprising these scales should be further tested as facilitators of physical activity participation in this population.

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Appendices

Paper I

Paper II

Paper III

Appendix A:	Non-Disclosure Agreement the Phys-Can study
Appendix B:	Sub-project Agreement The CRC-NORDIET study
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Paper I

How many days of continuous physical activity monitoring reliably represent time in different intensities in cancer survivors.

PLOS ONE

RESEARCH ARTICLE

How many days of continuous physical activity monitoring reliably represent time in different intensities in cancer survivors

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Abstract

Background

Physical activity (PA) monitoring is applied in a growing number of studies within cancer research. However, no consensus exists on how many days PA should be monitored to obtain reliable estimates in the cancer population. The objective of the present study was to determine the minimum number of monitoring days required for reliable estimates of different PA intensities in cancer survivors when using a six-days protocol. Furthermore, reliability of monitoring days was assessed stratified on sex, age, cancer type, weight status, and educational level.

Methods

Data was obtained from two studies where PA was monitored for seven days using the SenseWear Armband Mini in a total of 984 cancer survivors diagnosed with breast, colorectal or prostate cancer. Participants with ≥22 hours monitor wear-time for six days were included in the reliability analysis ($n = 736$). The intra-class correlation coefficient (ICC) and the Spearman Brown prophecy formula were used to assess the reliability of different number of monitoring days.

Results

For time in light PA, two monitoring days resulted in reliable estimates (ICC >0.80). Participants with BMI ≥25, low-medium education, colorectal cancer, or age ≥60 years required one additional monitoring day. For moderate and moderate-to-vigorous PA, three monitoring days yielded reliable estimates. Participants with BMI ≥25 or breast cancer required one additional monitoring day. Vigorous PA showed the largest within subject variations and reliable estimates were not obtained for the sample as a whole. However, reliable estimates

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were obtained for breast cancer survivors (4 days), females, BMI ≥30, and age <60 years (6 days).

Conclusion

Shorter monitoring periods may provide reliable estimates of PA levels in cancer survivors when monitored continuously with a wearable device. This could potentially lower the participant burden and allow for less exclusion of participants not adhering to longer protocols.

Introduction

Physical activity (PA) may improve health outcomes in cancer survivors, including fatigue, anxiety, depressive symptoms, physical functioning, and health-related quality of life [1]. As the field of exercise oncology is expanding, PA levels before, during, and after cancer treatment are increasingly measured and reported in cancer research [2, 3].

A wide range of instruments are currently used for measuring PA. Questionnaires are the most common approach for collect PA data as they are cost-effective and can be distributed to large samples [4]. However, self-reported PA is at risk of recall-, misclassification-, and social desirability bias, and cancer survivors are likely to overreport their activity level when using questionnaires [5, 6]. Objective assessments, in the form of wearable PA monitors, can provide more reliable PA estimates compared to questionnaires, but is also not without limitations. How PA data is collected and processed can impact the quality of the acquired data, and methods have been found inconsistent across studies of cancer survivors, especially regarding the number of days to monitor [7]. Furthermore, required monitor wear-time, encompassing both the number of days and hours per day to measure, are merely defined in half of the studies with the purpose of quantifying PA in cancer survivors through accelerometers [7]. While standardization of monitoring protocols can be advantageous for comparison and replication, it has been argued that the appropriate number of days to monitor PA is dependent on the research question [8, 9]. Generally, large sample sizes have been shown to require fewer monitoring days and produce lower standard errors of the mean (SEM), thus providing more reliable estimates, compared to smaller sample sizes with numerous monitoring days [9].

Extensive monitoring periods may be burdensome for some participants and could potentially lead to non-consent of study participation and non-adherence to monitoring protocols [10, 11]. The burden of study participation may be greater in persons with medical conditions also affected by the disease burden compared to healthy adults. Ideally, the monitoring protocol with the least participant burden and most reliable estimates would be the most appropriate. The number of days PA should be monitored to reliably represent time in PA intensities can be found by assessing the intra-individual and inter-individual variability in PA across monitoring days (i.e., the within- and between-subject variation). With increased day-to-day variation in PA within subjects, more monitoring days would be needed for reliable estimates representing a certain point in time.

In the general population, the reliability of number of monitoring days have been assessed in numerous studies based on various timeframes, daily wear-time, and sample sizes [12–23]. However, the results are inconclusive, reporting reliable estimates of moderate-to-vigorous PA (MVPA) with 2–10 monitoring days. The ambiguous results may relate to how many days' variability is considered, thus, the respective timeframes serving as the foundation for the reliability estimates. Also, the varying daily monitor wear-times ranging from 8–24 hours can

impact the variability in measured PA. Continuous wear of the monitors have only been assessed in a few studies, with the purpose of obtaining estimates representing absolute time in PA, limiting variance caused by differing wear-times [16, 17, 23]. With increasing technological developments of wearable PA devices including longer battery life and more comfortable designs and ease of use, allowing for continuous wear and monitoring, there is a need for studies utilizing such wear-time protocols. Reliability assessments of PA estimates in cancer survivors are scarce and no consensus exists on how many days to monitor, which have led to considerable inconsistency in monitoring protocols [2, 3, 7]. Three monitoring days have been found reliable in representing time in MVPA in colorectal cancer survivors >6 months post-surgery, with an accelerometer worn during waking hours [24]. However, no study has made these assessments for different PA intensities in a mixed sample of cancer survivors using continuous monitor wear-time, nor assessed whether participant characteristics impact the reliability.

The aim of the present study was to determine the minimum number of monitoring days for reliable estimates of time in different PA intensities in cancer survivors, using a continuous wear-time protocol. Furthermore, the reliability was assessed stratified on sex, age, diagnosis, weight status, and educational level.

Material and methods

Participants and study design

In the present study we harmonized baseline data from the Phys-Can study [25] and the CRC-NORDIET study [26]. The current hypotheses and statistical analyses were not prospectively registered, rather, application for use of the data was sent to the respective studies and processed and approved by the boards.

The harmonized dataset consisted of 984 participants diagnosed with either breast, colorectal or prostate cancer, stages I-III. The CRC-NORDIET study included participants with colorectal cancer who completed baseline 2–9 months post curative surgery (median 5.3 months), with approximately 1/5 also receiving post-surgery chemotherapy. The Phys-Can study included participants with colorectal, breast or prostate cancer who completed baseline before starting neoadjuvant or adjuvant therapy. In both studies, PA levels were measured using the SenseWear™ Armband Mini (SWAM) (BodyMedia Inc. Pittsburgh, PA, USA) and the same monitoring protocol was followed (i.e., the same instructions on how to wear the monitor and the continuous wear throughout seven days were provided).

Physical activity instrument

The SWAM is a multi-sensor device containing a tri-axial accelerometer and sensors measuring heat flux, galvanic skin response, skin temperature, and near-body ambient temperature. The SWAM has been validated for estimating total energy expenditure and showed promise in accurately measuring daily energy expenditure under free-living conditions as well as resistance training [27–29]. The original Sensewear Armband has previously been tested in cancer populations [30]. The SWAM was placed on the non-dominant upper arm.

Data management

A valid day of PA monitoring was defined as ≥22 hours wear of the monitor. Currently, there are no consensus on how long a monitor should be worn each day to produce reliable estimates. Thus, 22 hours representing >90% of a day, was chosen as we wanted to use continuous monitoring and absolute time in PA intensities, allowing for short periods of removal.

Raw data was handled using software developed by the manufacturer (Sensewear Professional Research Software Version 8.1, BodyMedia Inc., Pittsburgh, PA, USA). Metabolic equivalents (METs) were calculated based on the accelerometer and temperature sensors through algorithms in the SWAM software. METs were used for representing time in PA intensities. Light intensity PA (LPA) was defined as METs between 1.5 and 3. MET values of 3–6 corresponded with moderate intensity PA (MPA), while vigorous intensity PA (VPA) was established for MET values >6. Thus, MVPA corresponded with METs ≥3.

Within the monitoring week, the first day showed inadequate wear-time across the sample, as it was usually the day SWAM was administered to the participants. Thus, the first monitoring day was excluded from analyses and six days served as the criterion. For participants with more than six valid days, the first consecutive six days with sufficient wear-time were used.

The sample was further stratified on sex (male, female), age (<60 and ≥60), diagnosis (colorectal, breast, and prostate cancer), weight status (body mass index (BMI) <25, ≥25 <30, and ≥30), and educational level (low-medium and high). Low-medium education included primary and secondary school, while higher education included education at college or university level. Details on how these variables were measured have been reported elsewhere [25, 26]. Participant characteristics used for stratification were chosen based on their availability within the dataset, as well as their theoretical relevance related to PA level, and were hypothesized to also have potential impact on the variance in PA. No category representing underweight BMI was made as only eight subjects were below BMI 18.5 and were thus included in BMI <25.

Ethic statement

Written informed consent was obtained from all participants enrolled in the two studies. The Phys-Can study was approved by the Regional Ethical review Board in Uppsala, Sweden (protocol approval 2014/249) and registered in ClinicalTrials.gov (NCT02473003, Oct 2014). The CRC-NORDIET study was approved by the Reginal Committees for Medical and Health Research Ethics, Norway (protocol approval 2011/836), and the data protection officials at Oslo University Hospital and Akershus University Hospital, and registered in ClinicalTrial.gov (NCT01570010).

Statistical analyses

Differences in characteristics between participants with and without six valid monitoring days were assessed with independent sample t-tests for continuous variables, and the Pearson Chi-Square test for categorical variables.

The intra-class correlation coefficient (ICC) was used to study the variance in PA across the six days. The coefficient for "single measures" gives the relative contribution of inter-individual variance on the total variance and indicate the reliability of using one monitoring day to represent the monitoring period. The Spearman Brown prophecy formula for interrater reliability was applied to calculate the reliability of using the average of an increasing number of days to represent PA levels based on the measured six days [31–33]. The Spearman Brown prophecy formula was expressed as $((k \times r) \div (1+(k-1)\times r))$ where k is the number of days and r is the single measures coefficient [31, 32]. An ICC >0.80 was considered sufficient for reliable estimates [34].

Results from the one-way random (ICC(1)), the two-way random absolute agreement (ICC(A,1)) and two-way random consistency (ICC(C,1)) were compared to assess bias contribution to the total variance (Table 1 in S1 File) [35]. Bias contribution, as well as intra-individual and inter-individual contribution to the variance were calculated based on mean squares from the

ICC(A,1), and presented in (Table 3 in S1 File) [35]. Bias was found negligible (<1% of the total variance) and coefficients consistent across models.

Results were considered statistically significant for p-values <0.05. Analyses were conducted using SPSS 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.), while the Spearman Brown formula was calculated by hand.

Results

Of the 984 cancer survivors, 736 participants (74.8%) had ≥22 hours daily SWAM wear-time for six days or more and were included in the reliability analyses (Table 1). Their mean age and standard deviation (±SD) were 62.6 years (±10.5), with a mean BMI of 26.4 (±4.6). For the 248 excluded cancer survivors, age was significantly lower (59.8 years ±11.6, p<0.01) and BMI similar (25.8 ±4.3, p = 0.058). Various descriptive data were missing from 46 participants across the two groups for unknown reasons. Excluding them from the analyses did not alter the results and they were kept in the present analyses.

The ICC absolute agreement [95% confidence interval] for single measures was 0.690 [0.660, 0.716] for LPA, 0.606 [0.576, 0.636] for MPA, 0.378 [0.345, 0.412] for VPA, and 0.610 [0.580, 0.639] for MVPA.

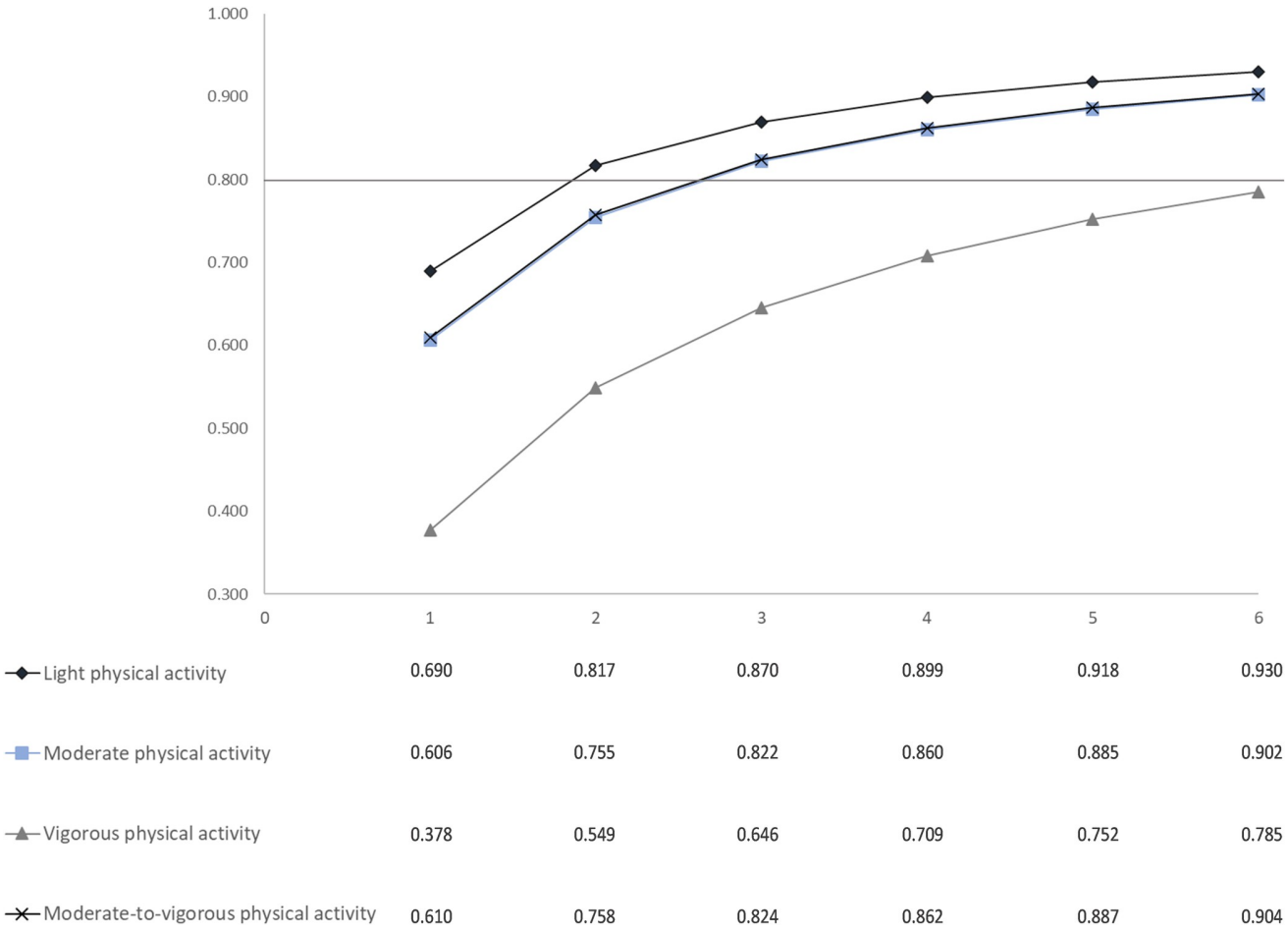

Fig 1. Number of monitoring days with the corresponding intra-class correlation coefficient (ICC) based on the Spearman Brown formula for each physical activity intensity (n = 736).

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Table 1. Descriptive statistics of cancer survivors with six valid measuring days (included) and without six valid days (excluded).

Characteristics	Included	Excluded	Difference
	n = 736	n = 248	
	n (%)	n (%)	
Sex			p = 0.827
Male	259 (35.2)	80 (32.3)	
Female	464 (63.0)	163 (65.7)	
Age			p = 0.011*
<60 years	250 (34.0)	106 (42.7)	
≥60 years	473 (64.3)	137 (55.2)	
Diagnosis			p = 0.009*
Breast cancer	289 (39.3)	125 (50.4)	
Colorectal cancer	366 (49.7)	107 (43.1)	
Prostate cancer	72 (9.8)	16 (6.5)	
Weight status			p = 0.420
BMI <25	292(39.7)	107(43.1)	
BMI ≥25 <30	280(38.0)	87(35.1)	
BMI ≥30	130(17.7)	37(14.9)	
Education			p = 0.232
Low-medium	302 (41.0)	108 (43.5)	
Higher education	406 (55.2)	121 (48.8)	

*significant difference between included and excluded participants.

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With the Spearman Brown formula, an ICC >0.80 was achieved with two monitoring days for LPA and three monitoring days for MPA and MVPA (Fig 1). No number of days within the six days timeframe resulted in an ICC >0.80 for VPA due to large intra-individual variance (Table 3 in S1 File).

The ICC and Spearman Brown formula were further calculated stratified on participant characteristics, which revealed some differences in reliability across the subgroups (Fig 2).

An ICC >0.80 was obtained for LPA with three monitoring days in participants with BMI ≥25, low-medium education, colorectal cancer, and age ≥60 years (Fig 2A). For MPA and MVPA, four monitoring days were required in participants with BMI ≥25 and breast cancer (Fig 2B and 2D). The need for additional monitoring days reflected a higher intra-individual variance in PA. For VPA, an ICC >0.80 was found using six monitoring days in females, breast cancer survivors, and participants <60 years, and with four days in participants with BMI ≥30, reflecting lower intra-individual variance in VPA (Fig 2C).

Discussion

In the present study we assessed the reliability of number of monitoring days representing time in PA intensities in cancer survivors. When accounting for the six-day variation in PA, two monitoring days for LPA, and three monitoring days for MPA and MVPA were sufficient for obtaining reliable estimates. The level of VPA was low, therefore the results for MVPA reflected that of MPA. The low level of VPA and high day-to-day variation within participants suggested that longer monitoring periods are necessary for obtaining reliable estimates. Six monitoring days were close to an ICC >0.80, which could imply that using seven or eight days will exceed the cut-off. However, we did not assess the reliability for a number of days exceeding six days, as our ICC was based on the six days variation. While assessments of more days

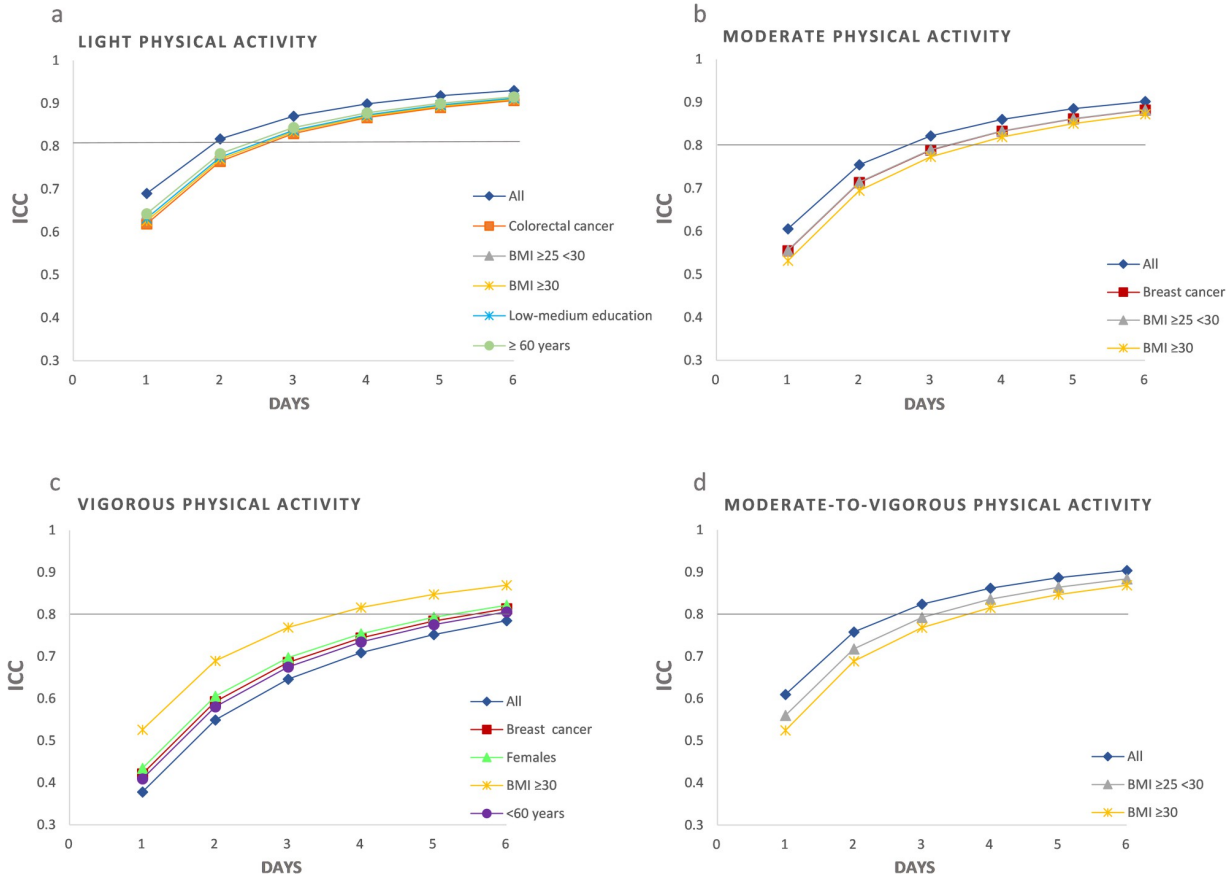

Fig 2. ICCs for each monitoring day in the total sample and in the stratified samples that deviated from the reliable number of days found for the whole sample of 736 cancer survivors. (a) Colorectal cancer survivors, participants with BMI ≥25, low-medium education, or ≥60 years old required an additional monitoring day for reliable estimates of LPA. (b) Four monitoring days were required for reliable estimates of MPA in participants with breast cancer or BMI ≥25. (c) While reliable estimates of VPA were not obtained for the total sample, participants with BMI ≥30 achieved reliable estimates with four monitoring days, and females, breast cancer survivors and participants <60 years old achieved reliable estimates with six monitoring days. (d) Participants with BMI ≥25 required four monitoring days for MVPA.

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may yield the same variance estimates, thus a similar ICC for one measuring day, it may also increase the intra-individual variance resulting in a lower ICC. In the stratified analyses, some participant characteristics had implications for the variance in PA, thus affecting the reliability.

Our results are in line with findings from a study where SWAM was used in the general population with the same daily wear-time of ≥22 hours [23]. In the study by Scheers et al., three monitoring days were necessary for obtaining an ICC >0.80 for LPA, MPA and MVPA in adults. Similarly, reliable estimates for MVPA using three monitoring days have been found in a smaller sample of colorectal cancer survivors [24]. Compared to the general population, it appears that cancer survivors may have similar or slightly lower intra-individual variability in LPA and MPA but higher variability in VPA [12–22].

To our knowledge, there has been no previous assessments of the impact of sex, age, cancer type, weight status or education on the reliability of monitoring days in cancer survivors. Moreover, underlying explanations for differences in intra-individual variation in PA have not been established. We did not account for external factors such as weather, weekends, or time of year, which could further account for the variance in PA. Such circumstances may have

affected participants with deviating levels of intra-individual variance relative to the total sample, to a lesser or greater extent.

Overweight and obese participants had both higher intra-individual variation in LPA, MPA and MVPA, and significantly lower levels of these intensities compared to normal-weight participants (Table 2 in S1 File). Their level of VPA was also low, but so was their day-to-day variance in VPA. This implies higher proportions of sedentary time and may suggest less planned PA, resulting in sporadic and spontaneous activity throughout the day. On the other hand, engaging in exercise (structured or planned PA) some days of the week can result in higher day-to-day variations compared to individuals who do not exercise. However, the relatively low levels of PA across intensities in overweight and obese participants suggested little engagement in exercise. Higher levels of MPA were associated with being male, having colorectal or prostate cancer, age <60 years, and BMI<25 (Table 2 in S1 File). Higher levels of VPA were associated with age <60 years, higher education, and BMI <25.

The measured activity levels in our study were above the recommended weekly 150 minutes MVPA (Table 2 in S1 File). However, this minimum threshold may not be appropriate when using continuous PA monitoring protocols [14]. In previous studies, researchers have documented how feedback from sophisticated wearable devices worn continuously is incompatible with current PA recommendations and can make people erroneously form the view that they are exceeding recommendations by several fold if adjustments are not made [36]. For MVPA, 1000 minutes weekly, representing 15% of waking time, has been suggested as a more appropriate target when using continuous monitoring [36]. However, it is possible that some participants increased their activity levels as a result of being monitored.

Strengths and limitations

With this study we were the first to assess the number of monitoring days required for reliable PA estimates in cancer survivors using continuous monitoring. When studying variability in PA levels, having a mixed sample means we may account for more of the variation in PA caused by heterogeneity in the sample. As our sample varied in cancer type, age, sex, socio-economic background, and weight status, together with the large sample size, we may have been able to account for some of the heterogeneity within the cancer population that might cause variations in PA levels. The included variables were chosen based on their availability within the harmonized dataset and their theoretical relevance for PA. However, we did not account for all other relevant covariates which could have further impacted and explained the variation in PA, e.g., treatment type, time since treatment, physical function, fatigue, or cancer stage. Information on treatment type, time since treatment and cancer stage were not sufficient for harmonization. While all participant in the Phys-Can study were assessed before starting neoadjuvant or adjuvant treatment, participants in the CRC-NORDIET study were recruited post curative surgery. About 10% of the CRC-NORDIET participants received pre-surgery radiotherapy or chemoradiotherapy, while about 20% received post-surgery chemotherapy, but lacked information on the duration and number of cycles. This limited the possibility of harmonizing on treatment type and time since treatment. Cancer stage was only available for one study.

Furthermore, we only accounted for the variation in PA across six days, thus reported how well different number of monitoring days represented the observed variation within this timeframe. We do not know whether this variation is consistent across longer monitoring periods. Thus, further research should assess the variability in PA across longer time spans using continuous monitoring in order to establish a reliable number of monitoring days representing longer time periods.

Using cut-offs for acceptable reliability has its limitation and may not be appropriate in all settings. We obtained an ICC of 0.785 for VPA which would have been regarded as sufficient when using a cut-off around 0.7–0.75 as some researchers have previous suggested [16, 34]. All coefficients were listed in (Table 3 in S1 File) under *Inter-individual variance contribution* and can be utilized if different cut-offs are of interest.

Implications for future research

Researchers should note that some participant characteristics can have implications for the variance in PA affecting how many days some cancer survivors should be monitored in order to obtain reliable estimates. Also, within subject variance in PA can vary independently of PA level. Whether variance in PA and thus the reliability of monitoring days is affected by cancer specific factors including cancer stage, treatment type, symptoms, and late effect, needs further exploring. VPA showed particularly large day-to-day variations within cancer survivors which means that longer monitoring periods may be necessary for obtaining reliable estimates of time spent in VPA. The variation in VPA across longer periods of time and how this affects the reliability should be further assessed. We chose a daily monitor wear-time of $\geq$22 hours to limit the effect of wear-time on the variance in PA, which has also been applied in previous research using SWAM [23]. However, there is no consensus on how many hours daily a PA monitor should be worn in cancer survivors in order to constitute a valid day, and researchers often use different ways of defining a valid monitoring day [37]. When and how many hours daily PA monitors should be worn to obtain reliable estimates of daily PA, and how the reliability of monitoring days is affected by different wear-time cut-offs should be further explored. PA monitors able to accurately distinguish between non-wear-time, sleep, and sedentary time, should be used to assess the number of days required for reliable estimates of sedentary time in cancer survivors.

Perspectives

In the present study, 941 (95.63%) cancer survivors had at least three out of seven days with $\geq$22 hours SWAM wear-time, complying with the minimum of three days found necessary for reliable estimates of LPA, MPA and MVPA. This demonstrates how measurements from more participants relative to the 74.8% complying with the 6-days protocol could have been utilized in a study when assessing their PA levels. Employing a shorter monitoring protocol may possibly facilitate study participation and lower the participant burden. From a researcher perspective, when deciding on an appropriate monitoring period, it should be considered how sex, cancer type, age, education, and weight status are associated with variations in PA. Though intra-individual variance in MPA appears similar to the general adult population, cancer survivors may have lower intra-individual variance in LPA and higher intra-individual variance in VPA.

Conclusion

In the present study, we assessed the variance in physical activity level across six days with continuous monitoring in breast, colorectal, and prostate cancer survivors 0–9 months post treatment. Based on the observed variance, two monitoring days for light physical activity, and three days for moderate and moderate-to-vigorous physical activity were required for reliable estimates in the total sample. Intra-individual variation in vigorous physical activity was greater and more than six monitoring days appeared necessary for reliable estimates. In the stratified analyses, one additional monitoring day was required for reliable estimates of light physical activity in cancer survivors with colorectal cancer, BMI $\geq$25, low-medium education,

or age ≥60 years. One additional monitoring day was required for moderate physical activity in cancer survivors with breast cancer or BMI ≥25, while one additional day was required for moderate-to-vigorous physical activity with BMI ≥25. Reliable estimates of vigorous physical activity were obtained for cancer survivors with BMI ≥30, breast cancer, age <60, and for females.

Supporting information

S1 File. Contains supporting tables.
(DOCX)

S1 Dataset.
(SAV)

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Paper II

Dropout from exercise trials among cancer survivors - An individual patient data meta-analysis from the POLARIS study.

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ORIGINAL ARTICLE

WILEY

Dropout from exercise trials among cancer survivors—An individual patient data meta-analysis from the POLARIS study

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Abstract

Introduction: The number of randomized controlled trials (RCTs) investigating the effects of exercise among cancer survivors has increased in recent years; however, participants dropping out of the trials are rarely described. The objective of the present study was to assess which combinations of participant and exercise program characteristics were associated with dropout from the exercise arms of RCTs among cancer survivors.

Methods: This study used data collected in the Predicting OptimaL cAncer RehabIlitation and Supportive care (POLARIS) study, an international database of RCTs investigating the effects of exercise among cancer survivors. Thirty-four exercise trials, with a total of 2467 patients without metastatic disease randomized to an exercise arm were included. Harmonized studies included a pre and a posttest,

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For Affiliation refer page on 8

and participants were classified as dropouts when missing all assessments at the post-intervention test. Subgroups were identified with a conditional inference tree.

Results: Overall, 9.6% of the participants dropped out. Five subgroups were identified in the conditional inference tree based on four significant associations with dropout. Most dropout was observed for participants with BMI >28.4 kg/m^2, performing supervised resistance or unsupervised mixed exercise (19.8% dropout) or had low-medium education and performed aerobic or supervised mixed exercise (13.5%). The lowest dropout was found for participants with BMI >28.4 kg/m^2 and high education performing aerobic or supervised mixed exercise (5.1%), and participants with BMI ≤28.4 kg/m^2 exercising during (5.2%) or post (9.5%) treatment.

Conclusions: There are several systematic differences between cancer survivors completing and dropping out from exercise trials, possibly affecting the external validity of exercise effects.

KEYWORDS

cancer, decision tree, exercise oncology, individual patient data meta-analysis

1 | INTRODUCTION

Exercise has been associated with reduced cancer morbidity and mortality, improved physical fitness, reductions in fatigue, better management of treatment side effects, and better quality of life among individuals living with and beyond cancer, herein defined as cancer survivors.[1–5] The number of randomized controlled trials (RCTs) investigating the effects of exercise on a variety of outcomes among cancer survivors, spanning the pretreatment, treatment, and posttreatment phases has increased in recent years.[6] The exercise programs in such trials vary considerably in terms of the tested modality and delivery format, as well as frequency, duration, timing, and intensity of the exercise. Findings from these heterogeneous trials support statistically significant and clinically relevant benefits through participation in exercise programs.[7] However, evidence for the harms of exercise in some cancer populations is uncertain due to high risk of bias, poor reporting, and lack of trials.[8] A potentially higher risk of some harms during exercise interventions among cancer patients undergoing systemic treatment has recently been reported.[8] Systematic differences between participants who complete or drop out of RCTs may introduce bias to the findings and conclusions through missing data.[9,10] Participants dropping out may be underrepresented in the analyses, or their incomplete data can influence the size of observed effects. Consequently, findings may lack broad applicability and external validity if the missing data is not random. Reasons for not completing follow-up assessments could be withdrawal, not showing up to the study assessments, or exclusion. However, exercise intervention dropout, as defined by not completing follow-up assessments, does not provide insight into the intervention adherence.

The reported proportions of cancer survivors dropping out of exercise trials vary widely, ranging from none or only a few percent[11,12] to as high as 30%–45%.[13,14] The large differences in the number of participants dropping out of various exercise trials may partially be due to the difference in how these cases are defined and reported. While reasons are sometimes provided for why a participant did not complete study assessments, the type of missingness and how the missing data may bias the results are seldomly explained.[14,15] However, sample sizes of individual studies are often too small to identify associations with study dropout and rarely allow for comparisons of different exercise programs. If dropout is significantly associated with certain characteristics, the conclusions about intervention efficacy may be biased and the generalizability compromised. Identifying cancer survivors more likely to drop out from the exercise arms may further suggest targets where barriers and facilitators of trial completion must be identified.[13,16]

In the current study, we used individual patient data collected as part of the Predicting OptimaL cAncer RehabIlitation and Supportive care (POLARIS) study.[17] POLARIS is the largest set of individual patient data from RCTs investigating the effects of exercise in a mixed sample of cancer survivors. It thereby provides a unique opportunity to examine participants dropping out of the exercise arms across various trials. The objective of

the present study was to assess which combinations of participant and exercise program characteristics were associated with higher levels of dropout among cancer survivors.

2 | MATERIALS AND METHODS

2.1 | Study design

The present study used individual patient data available via the POLARIS study, an international infrastructure and shared database of RCTs investigating the effects of exercise interventions in cancer survivors on a range of outcomes (registered in PROSPERO, CRD42013003805). A detailed description of the POLARIS study design, including the method of study identification and selection, and details on requested variables have been published elsewhere.[17] All individual studies in the database were conducted in line with the principles of the Declaration of Helsinki and received approval from their local ethics committees. Informed consent was obtained from all participants included in the individual studies. For the current analyses, we included cancer survivors who completed baseline assessments and were randomized to the exercise arms of the trials (34 RCTs, $n = 2514$). We excluded participants with metastatic disease due to the small sample size, and the possibility of differential effects on dropout ($n = 47$).

2.2 | Outcome assessment

The individual patient data contained two measuring points: Baseline and post-intervention. If trials included more than one post-intervention follow-up, the first follow-up after the intervention was finished, was included. Dropout was established when all data were missing at follow-up,[9] i.e., when participants did not complete any of the post-intervention assessments. All available variables in each original study were assessed for missing data post-intervention although only harmonizable variables related to the research question (participant and exercise intervention characteristics) were included. Information about exercise intervention adherence was not available, thus, the definition of dropout addressed missing data independent of adherence.

2.3 | Participant characteristics

Participant characteristics included age, sex, educational level, body mass index (BMI, kg/m^2), cancer type, and treatment. Educational level was dichotomized into low-medium (elementary, primary or secondary school, or lower or secondary vocational education) and high (higher vocational, college or university education).

Treatment with surgery, chemotherapy, radiotherapy, hormone therapy or stem cell transplantation were each dichotomized into previously or currently receiving this treatment versus not receiving this treatment. However, as numerous different combinations of treatment received were not feasible to assess, they were not included in the final model.

2.4 | Exercise intervention characteristics

Intervention characteristics included timing (during or posttreatment), exercise type (supervised aerobic, unsupervised aerobic, supervised resistance, supervised mixed, or unsupervised mixed), exercise intensity (low-moderate, moderate, moderate-vigorous, or vigorous), exercise session frequency (number of weekly exercise sessions), exercise session duration (≤30 min, >30 to ≤60 min, and >60 min), and intervention duration (≤3 months, >3 to ≤6 months, >6 months). Mixed exercise type included programs that had both an aerobic and a resistance exercise component. None of the included RCTs contained only unsupervised resistance exercise, and no intervention was carried out before treatment (Appendix S1).

Intervention timing was defined in line with previous POLARIS publications.[2] As hormone therapy for breast cancer may continue for several years posttreatment, women on hormone therapy who completed other primary cancer treatments were considered as being posttreatment. Men receiving androgen deprivation therapy for prostate cancer were considered as being during treatment.

2.5 | Missing data

For two studies, individual patient data on program duration were not available. One reported the median program duration (17 weeks, i.e., 3–6 months), which was added for this sample ($n = 160$).[18] The other study reported an overall range for program duration, which spanned from <3 months to 3–6 months.[19] Thus, this sample ($n = 40$) was randomly divided into two groups where <3 months was added for one half and 3–6 months for the other half. In the final dataset, there were some missing values for exercise program timing (0.1%), age (0.4%), session duration (2.8%), session frequency (5.3%), BMI (9.9%), exercise intensity (10.7%), and educational level (12.9%).

2.6 | Statistical analysis

Standardized effect sizes for the difference in or distribution of independent variables between participants dropping out or completing the exercise arms of the studies were reported with Cohen's d for continuous predictors, Cramer's V for nominal predictors, and Kendall's tau-b for ordinal predictors. Statistically significant *p*-values ($p < 0.05$) based on the independent sample *t*-test or chi square test were added.

With large sets of variables, complex, nonlinear and multilevel interactions can be challenging to assess and interpret through multivariable regression analysis.[20,21] As a parsimonious alternative, we applied the conditional inference tree (Ctree) to the dataset with dropout as the binary outcome. The Ctree algorithm can handle a large number of variables by performing multivariable assessments simultaneously and identifies the main and interactive effects explaining the most variability in the outcome.[22] The Ctree algorithm performs binary splits based on the predictors most strongly associated with the outcome, with a significance level of $p < 0.05$.[22] When splitting on continuous predictors, the splitting value is data driven and chosen based on the split that maximizes the statistical significance and "purity" of the new nodes, creating the most variability in the outcome. Cases with missing values on the split variable were allocated randomly to a node. The Ctree was conducted in R (version 4.1.1) with the "partykit" package.

3 | RESULTS

From the 34 original exercise trials (with a total of 4519 participants) included in the POLARIS database, 2467 participants without metastatic disease were randomized to an exercise arm. The number of participants included in the exercise arm of each original study varied from eight to 218, with a median of 53 (Appendix S1). Overall, 9.6% of the cancer survivors participating in the exercise arms dropped out but ranged from zero to 34.3% across the studies (Table 1).

Five subgroups of cancer survivors were identified based on four characteristics (Figure 1). These were BMI, with a split value of 28.4 kg/m^2 in the total sample, timing of the exercise intervention in the BMI ≤28.4 kg/m^2 subsample, and exercise type and educational level in the BMI >28.4 kg/m^2 subsample. The Ctree *p*-values for each split including all predictors with weaker but significant associations with dropout, hence not used for splitting, are presented in Appendix S2.

The lowest proportions of dropouts (5.1% and 5.2%, respectively) were observed for participants with BMI >28.4 kg/m^2, who performed aerobic or supervised mixed exercise and were highly educated, and participants with BMI ≤28.4 kg/m^2 who exercised during treatment (Figure 1). Among participants with BMI ≤28.4 kg/m^2 who exercised posttreatment, 9.5% dropped out. The highest proportions of dropouts (13.5% and 19.8%, respectively) were observed for participants with BMI >28.4 kg/m^2, who either performed aerobic or supervised mixed exercise and had a low-medium educational level or performed supervised resistance or unsupervised mixed exercise. Nine and four harmonized RCTs included only resistance exercise or unsupervised mixed exercise, respectively (≈38% of the RCTs).

4 | DISCUSSION

This study examined the characteristics of cancer survivors and exercise programs showing significantly higher levels of study drop out. While 9.6% of the cancer survivors dropped out overall, we observed large differences in dropout between identified subgroups, ranging from 5.1% to 19.8% across the five subgroups. Although BMI showed the strongest association with dropout in the total sample, with more dropout in the higher BMI subsample, the Ctree algorithm identified great differences within this subsample. Cancer survivors with high BMI who participated in resistance exercise interventions or unsupervised mixed interventions were more likely to drop out than those who participated in aerobic or supervised mixed interventions. However, among the participants of aerobic and supervised mixed interventions, the dropout rate was substantially higher among those with low educational levels.

Although there are currently few RCTs in the cancer population assessing resistance exercise only, more cancer survivors have been found to drop out of resistance exercise interventions relative to aerobic exercise interventions.[14,23] In the present sample, this appeared to apply only to cancer survivors with higher BMI. This could be related to being less familiar with performing resistance exercises, side effects from the exercise (e.g., soreness), or the need to travel to the facilities as all sessions were supervised. As there were no unsupervised programs with resistance exercise only in the present dataset, it is unclear whether unsupervised resistance exercise could result in a higher or lower probability of dropping out. Unsupervised mixed exercise did show higher dropout than supervised mixed in the higher BMI sample, suggesting that supervision of the exercise sessions increased the likelihood of completing the exercise arms of studies. However, this needs further exploration, as it may be dependent on the type of exercise performed. More complement of, and

TABLE 1 Characteristics of participants dropping out or completing the studies.

	Dropped out, $n = 236$	Completed study, $n = 2231$	Effect size
	Mean (SD)	Mean (SD)	Cohen's d
Age	53.9 (12.8)	54.8 (11.3)	−0.080
BMI	28.9 (5.6)	26.9 (4.9)	0.507**
Prescribed exercise session frequency (weekly)	3.0 (1.7)	3.2 (1.6)	−0.126
	n (%)	*n* (%)	Cramer's V
Total	236 (9.6)	2231 (90.4)	
Sex			
Female	184 (78.0)	1743 (78.1)	0.001
Male	52 (22.0)	488 (21.9)	
Educational level			
Low-Medium	130 (55.1)	1016 (45.5)	0.075**
High	70 (29.7)	933 (41.8)	
Missing	36 (15.3)	282 (12.6)	
Cancer type			
Breast	170 (72.0)	1574 (70.6)	0.044
Male genitourinary	34 (14.4)	280 (12.6)	
Gastrointestinal	10 (4.2)	131 (5.9)	
Hematological	13 (5.5)	186 (8.3)	
Other	9 (3.8)	60 (2.7)	
Timing			
During treatment	94 (39.8)	1160 (52.0)	0.069**
Posttreatment	140 (59.3)	1070 (48.0)	
Missing	2 (0.8)	1 (0.0)	
Type of exercise			
Supervised aerobic	10 (4.1)	253 (11.3)	0.085*
Unsupervised aerobic	35 (14.8)	384 (17.2)	
Supervised resistance	70 (29.7)	480 (21.5)	
Supervised mixed	76 (32.2)	732 (32.8)	
Unsupervised mixed	45 (19.1)	382 (17.1)	
			Kendall's tau-b
Prescribed exercise session duration			
≤30 min	63 (26.7)	840 (37.7)	0.054*
>30 to ≤60 min	146 (61.9)	1106 (49.6)	
>60 min	22 (9.3)	221 (9.9)	
Missing	5 (2.1)	64 (2.9)	
Prescribed program duration			
≤3 months	73 (30.9)	755 (33.8)	0.047*
>3 to ≤6 months	70 (29.7)	836 (37.5)	
>6 months	93 (39.4)	640 (28.7)	
Intensity			
Low-moderate	17 (7.2)	150 (6.7)	−0.007
Moderate	90 (38.1)	767 (34.4)	
Moderate-vigorous	87 (36.9)	898 (40.3)	
Vigorous	24 (10.2)	171 (7.7)	
Missing	18 (7.6)	245 (11.0)	

*$p < 0.05$. **$p < 0.001$.

Abbreviations: BMI, body mass index; SD, standard deviation.

Note: Low-medium–elementary, primary or secondary school, or lower or secondary vocational education; High–higher vocational, college or university education; Mixed exercise—participants performed both aerobic and resistance exercise.

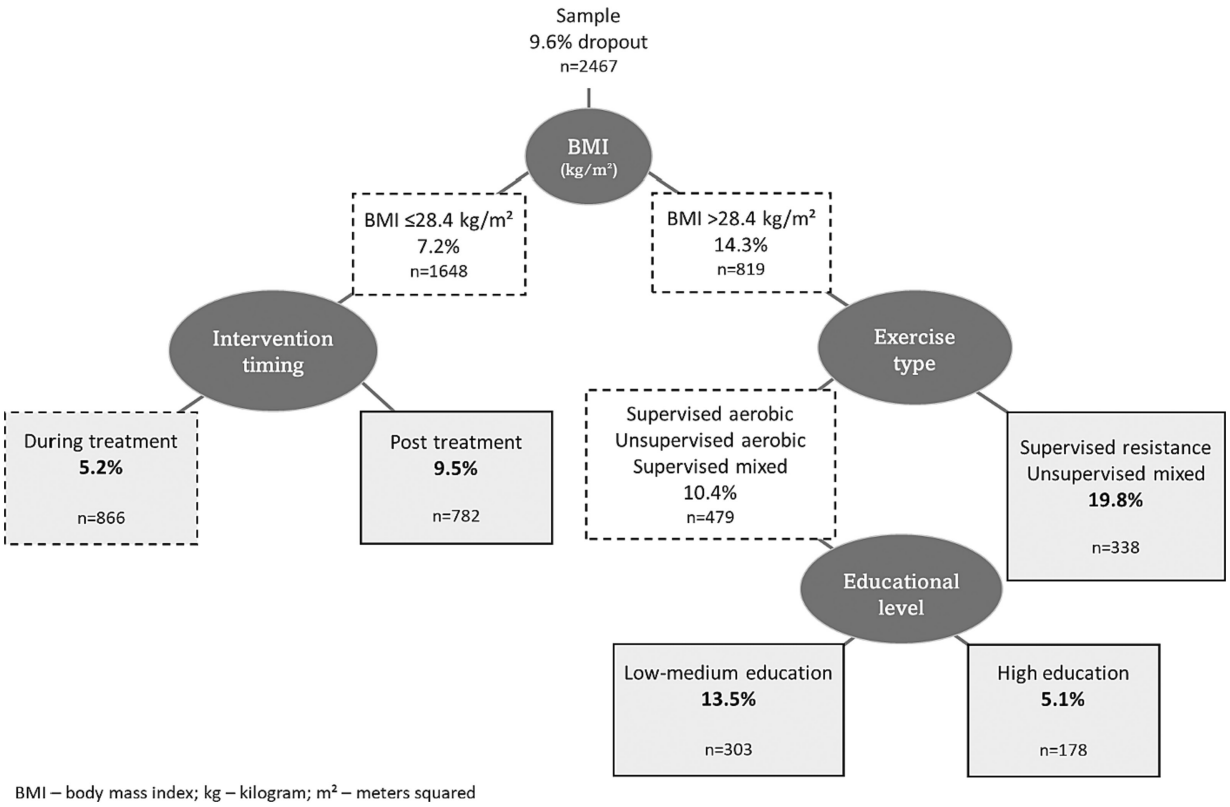

FIGURE 1 The conditional inference tree of associations with dropout. The circles represent variables with the strongest association with dropout in the total sample and subsamples. The dashed boxes represent subsamples where further associations with dropout were observed. The solid boxes represent the final subgroups where no further significant associations were observed. The percentages represent the proportions of participants dropping out in each subsample and subgroup.

compliance to, exercise interventions among cancer survivors have been previously reported for supervised compared to unsupervised programs.[14,24] Supervised exercise has also shown larger effects compared to unsupervised exercise for several outcomes.[1,25] Because cancer survivors with higher BMI were significantly more likely to drop out from resistance and unsupervised mixed exercise programs, they may be underrepresented when the effects of these interventions are assessed. Reasons for the higher dropout rate need further exploring, especially as resistance exercise is important for improving key health outcomes, including increased muscle mass, strength, and physical function.[26–28]

Having a high educational level was associated with a decreased probability of dropping out among participants with higher BMI who did not participate in resistance exercise intervention. A higher educational level has previously been associated with higher physical activity levels, decision-making abilities, health literacy, and a willingness to participate in exercise programs.[29–31] It is possible that a higher educational level was associated with factors increasing the probability of performing the interventions, leading to more completion of post-intervention assessments. Knowledge about exercise and exercise skills have previously been reported as predictors of exercise intervention adherence among cancer survivors,[32] and future studies should identify whether this or factors associated with knowledge and skills of exercise may also reduce dropout. Furthermore, it is possible that participants with a higher educational level were more motivated to exercise, and therefore endured the study period, due to more knowledge about benefits, higher levels of self-efficacy, more positive outcome expectations, and greater receptivity towards exercise.[33] However, there may have been other reasons for why cancer survivors with low-medium educational level in the higher BMI subsample were more likely to drop out. Factors such as other obligations, travel distance and transportation, comorbid health conditions, or lack of support may have influenced dropout.[32,34] Barriers for completing exercise trials should be further studied among cancer survivors with high BMI and low-medium education, as well as means to overcome these barriers.

In the subgroup of participants with lower BMI, we observed more dropout from exercise arms of trials conducted post cancer treatment compared to during cancer treatment. Although individuals undergoing cancer treatment are generally expected to be more ill due to

treatment side-effects, they may also be more motivated to make healthy changes to their behavior and lifestyle, to actively contribute to the treatment outcome themselves, or to receive additional support or monitoring from their health care professionals.[35,36] Cancer survivors who had completed treatment may have prioritized their time differently, not wanting to focus on their cancer diagnosis, but rather return to their everyday life, and thus not prioritizing completing the study assessments. Other roles and responsibilities and lack of time have previously been reported by cancer survivors as barriers to physical activity participation.[34] In contrast to our findings, lower BMI has previously been associated with more dropout from exercise programs performed during cancer treatment.[37] However, it is likely that this association was related to the frailty of the participants, more advanced cancer, and possibly cancer cachexia.[37]

It is concerning that the reporting of adverse events in exercise oncology trials is poor and possibly subject to publication bias.[8] Adverse events caused by the exercise may impact study dropout and should be reported to inform future interventions and the need for tailored programs. In the present study, information about adverse events was not available, thus, we do not know whether adverse events were experienced by those dropping out.

The variables age, sex, cancer type, exercise intensity, and weekly number of exercise sessions were not significantly associated with dropout in any steps of the Ctree. Session duration was significantly associated with dropout in the total sample and the BMI >28 kg/m^2 subsample (Appendix S2), but BMI and exercise type yielded a stronger association, thus, session duration was not used for splitting.

4.1 | Strengths and limitations

Our study has a number of strengths. By analyzing individual patient data (i.e., utilizing information of each participant rather than relying on summary statistics), we could improve the accuracy of the estimated associations by preserving individual characteristics.[38,39] Pooling data from numerous exercise trials allows for assessments of dropouts, which may be too small of a sample size to assess in individual studies. It also allows for assessments considering exercise intervention design and modalities. Machine learning techniques, including decision trees, are better at identifying relevant subgroups and nonlinear interactions from a statistical perspective compared to more traditional statistical methods.[21,40] It may also provide more intuitive and easily interpretable results. The Ctree gave a more detailed overview of significant associations with dropout by showing how associations in the total sample remained significant in some subsamples and not in others (Appendix S2). Such data-driven approaches can discover patterns and associations that may be complex and not evident through pre-specified models, and can be used to generate hypotheses and guide further research. When the variable chosen for splitting the Ctree has many cases with missing values who are randomly allocated to one of the new nodes, the Ctree can change when repeated. Repeating the algorithm with the present data did not change the significant variables, although small changes in subsample size, dropout rates, and *p*-values were observed.

Our study also had limitations that should be noted. First, although the POLARIS database is a large collection of individual patient data, the number of included trials is still small compared to the available literature. The harmonized sample was also largely made up of breast cancer survivors followed by male genitourinary cancer, although we had no restriction on cancer type. This limits the generalizability of our results to all exercise trials and cancer populations. However, dropout rates did not appear significantly different between breast and prostate cancer survivors. The research design of the trials, such as whether it was a pilot trial, or an exploratory, pragmatic, or implementation study was not included in the assessments. Second, decision trees can be used to obtain (nearly) pure nodes that can be used to predict the outcome in new samples. We did not test the predictive ability of our Ctree; however, the purpose of the present study was to describe significant associations with dropout and show interactions between the variables, not to classify individuals or predict dropout in new samples. Nevertheless, data-driven approaches can be at risk of overfitting, which limits the generalizability to new data. Thus, interpretations of the present findings should consider the exploratory nature of the analysis. Third, relevant associations or underlying explanations for why participants dropped out were likely missed. We did not assess psychosocial factors related to stress, depression, anxiety, motivation, self-efficacy, or previous exercise habits, which could further add to our understanding of why some cancer survivors drop out of exercise trials. Cancer stage was also not included, as this information was not available for a large part of the sample. Due to the limited number of participants with distant metastasis we were only able to focus on patients treated with curative intent, the results can therefore not be generalized to all patients with cancer. Fourth, all possible interactions between included variables were not described in the Ctree because the variable with the strongest association was used for splitting in each subsample. Thus,

splitting on variables with the second strongest association could have led to different interactions. Finally, we did not consider those declining intervention participation in the first place or assessed dropout in the control groups. Likely, there was already a bias in the initial sample caused by differences in characteristics between study participants and decliners, and the level of, and associations with, dropout could be different in the control groups. Further research should assess whether data missing not at random also occur among control groups.

4.2 | Perspectives

The present findings should be considered when designing, conducting, and generalizing results from exercise trials in the oncology setting. Further research is needed to understand the reasons for why specific subgroups of cancer survivors exhibit a greater tendency to drop out and to investigate possible facilitators to improve completion of the exercise arms. Future studies including different trials should also report and account for differences in study design when assessing dropout.

5 | CONCLUSIONS

Of the 2467 cancer survivors exercising in 34 RCTs, 9.6% dropped out. Five subgroups within the sample were identified, characterized by BMI, program timing, exercise type, and educational level, with dropout ranging from 5.1% to 19.8%. Participants most likely to drop out included those with BMI >28.4 kg/m^2 who either participated in resistance or unsupervised mixed exercise trials or had low-medium education and performed aerobic or supervised mixed exercise. These subgroups may require additional support to complete exercise interventions. Further research should explore possible reasons for why certain cancer survivors drop out and means to improve this.

AUTHOR CONTRIBUTIONS

LMB, MFK, and AEH contributed to the harmonization and handling of the POLARIS data. BW, LMB, SB, IV, and ID contributed to the conceptualisation and design of the present work. BW drafted the work, conducted and interpreted the present analyses, and revised the manuscript upon feedback from coauthors. AI made substantial contributions to the interpretation of the data and analyses. NKA, GR, MvB, MB, KC, AJD, DAG, RG, MMG, KAG, WHvH, SCH, FHR, MLI, EJ, MJK, HK, AL, AMM, AMC, WvM, NM, RUN, FN, HSO, RP, MES, KS, KHS, CES, GSS, KS, MMS, DRT, LT, MJV, JW, KMWS, JW, and LMB made substantial contributions to the design of the included RCTs, acquisition and handling of the data, and approved sharing of the data with the POLARIS database. All authors critically revised the work, contributed with valuable insight, and approved the final version of the manuscript.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Western B, Ivarsson A, Vistad I, et al. Dropout from exercise trials among cancer survivors—An individual patient data meta-analysis from the POLARIS study. *Scand J Med Sci Sports*. 2024;34:e14575. doi:10.1111/sms.14575

Appendix A

Non-Disclosure Agreement the Phys-Can study

UPPSALA
UNIVERSITET

FÖRSÄKRAN OM TYSTNADSPLIKT

Härmed försäkrar jag, att jag inte kommer att obehörigen yppa information, som jag fått genom PhysCan-projektet, som rör enskilda patienters/studiedeltagares personliga förhållanden eller hälsa. Denna försäkran styrs av Offentlighets- och Sekretesslagen och gäller både under den tid jag hanterar data inom projektet och därefter.

Kristiansand den 27.04.21

Namnteckning Benedikte Western

Namnförtydligande BENEDIKTE WESTERN

Tystnadsplikt och sekretess

Alla som arbetar inom hälso- och sjukvården, både offentlig och privat, arbetar under sekretess och tystnadsplikt. Det innebär att alla uppgifter som rör patientens personliga förhållanden skyddas av sekretess och får enbart lämnas ut efter särskild prövning.

Den som bryter mot tystnadsplikten kan dömas i domstol eller på andra sätt bli föremål för åtgärder av de myndigheter som har tillsyn över vården. Om patienten själv går med på det eller om det står klart att patienten eller någon närstående inte lider men av att uppgifterna lämnas ut kan sekretessen och tystnadsplikten brytas. Därutöver får uppgifter bara röjas i enlighet med särskilda sekretessbrytande bestämmelser i lag eller förordning. Det kan gälla situationer då uppgifter begärs ut av vissa myndigheter eller situationer där personalen har anmälningsskyldighet, till exempel om ett barn riskerar att fara illa.

Offentlighets- och sekretesslagen samt Patientsäkerhetslagen

Sekretessen regleras av offentlighets- och sekretesslagen för dem som arbetar inom staten, landstingen och kommunerna medan de som arbetar hos en privat vårdgivare ska följa reglerna om tystnadsplikt i patientsäkerhetslagen. Innebörden av dessa regler är dock mycket lika.

Alla inom vården har tystnadsplikt

När man som patient vänder sig till vården är det viktigt att man känner förtroende för den personal man möter. Förtroendet är viktigt för att man ska känna sig trygg och våga prata öppet om de besvär eller symtom man har och på så sätt få den vård man behöver. Därför omfattas alla som arbetar inom hälso- och sjukvården av tystnadsplikt. Grundprincipen är att ingen inom vården får lämna ut uppgifter utan att man själv har godkänt det. Det gäller till exempel uppgifter om den sjukdom man har, den behandling man får eller om ens privata situation.
Inom sjukvården gäller samma sekretesskydd för alla patienter och oberoende av om man har rätt att vistas i Sverige eller inte.

Tystnadsplikten gäller all personal som man möter i vården. Oavsett om det är inom offentlig eller privat vård och oavsett om det är läkare, sjuksköterskor eller administrativ personal. Tolkar och översättare som arbetar på uppdrag inom hälso- och sjukvården har också tystnadsplikt. Tystnadsplikten gäller även dem som arbetar på apotek.

Också mellan personal på ett sjukhus eller en vårdcentral finns en skyldighet att respektera patientens integritet. Som huvudregel är det bara de som deltar i vården av en patient som får prata med varandra om patientens hälsotillstånd eller personliga förhållanden.

Appendix B

Sub-project Agreement The CRC-NORDIET study

Avtale om delprosjekt i

Typisk norsk-studien (TNS)

Navn på søker/delprosjektansvarlig	Benedikte Western
Tilhørighet/institusjon	Universitetet i Agder
Kontaktopplysninger (e-post/tlf)	Benedikte.western@uia.no
Arbeidstittel delprosjekt	Methodological considerations with respect to physical activity monitoring in cancer survivors
Forslag til forfattere	Benedikte Western [1] Bjørge H. Hansen [1] Ingrid Demmelmeier [1 2] Ingvild Vistad [3 4] Karin Nordin [2] Rune Blomhoff [5 6] Hege Henriksen [5] Cecilia Arving [2] Sveinung Berntsen [1] [1]Department of Sport Science and Physical Education, University of Agder, Norway [2]Department of Public Health and Caring Sciences, Uppsala University, Sweden [3]Department of Clinical Science, University of Bergen, Norway. [4]Department of Obstetrics and Gynecology, Sørlandet Hospital, Kristiansand, Norway.

	[5]Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Norway. [6]Division of Cancer Medicine, Oslo University Hospital, Norway [7]Department of Oncology and Medical Physics, Haukeland University Hospital, Bergen, Norway
Formål/hypotese for delprosjektet (ca 1/2 side)	
A. Primærdata som skal brukes som endepunkt i delprosjektet. B. Beskriv studietidspunkt (preoperasjon, baseline, 6 mnd, 12 mnd, 3 år, 5 år, 7 år, 10 år, 15 år) C. Dato for uttrekk av primærdata.	A. Baseline activity data from the SenseWear armband will be used to estimate the reliability of using different number of days to represent 7 days physical activity. The SenseWear data will be calculated for different measures of physical activity, including minutes in low, moderate, and vigorous intensity, minutes of inactivity, daily steps, metabolic equivalents, and energy expenditure. We hypothesize that different number of days will be necessary to reliably represent 7 days physical activity across measures. Furthermore, the reliability of different number of days will be explored for different wear-time cut-offs. Both primary and secondary data will be pooled and harmonized with data from two similar studies. B. Baseline data. C. As soon as possible, preferably April/May 2021.
A. Beskrivelse av kilde for primærdata (for eksempel prosjektets database, eksterne registre, egne analyser av biologisk materiale etc). B. Beskriv evt. behov for uttak av biobank.	A. Primary data, SenseWear data, will be extracted from the project's database. B. No biobank data will be used.

Andre datasett (sekundærdata) som skal brukes som forklaringsvariabler i dette delprosjektet (OBS: andre delprosjekter vil rapportere disse resultatene som primærdata).	Secondary analyses include analyses of associations with wear-time. The secondary data include background information (age, gender, BMI, education, marital status, work status and sick-leave, cancer type, treatment and time since diagnosis) comorbidities, health related quality of life (SF-36), and fatigue. The purpose of these analyses is to assess whether there are characteristics of cancer survivors having insufficient wear-time. We hypothesize that there are significant differences in physiological, sociodemographic and disease specific variables between subjects having longer SenseWear wear-time and adhere to the wear-time protocol, compared to subjects with shorter wear-time not adhering to the protocol.
Beskrivelse kilde for sekundærdata (prosjektets database, eksterne registre, egne analyser av biologisk materiale etc). Beskriv evt. behov for uttak av biobank.	Secondary data, will be extracted from the project's database.
Prosjektperiode (prosjektstart/slutt)	Start: April 2021 End: We plan for having a first draft by October 2021

Dersom dette delprosjektet innebærer nye analyser av biologisk materiale, forplikter delprosjektleder seg til å bidra til at alle slike analyseresultater (herunder beskrivelse av metoder) inkluderes i TNS-databasen senest på publiseringstidspunktet. Hensikten er at resultatene skal gjøres tilgjengelig for andre forskere innen TNS, for eksempel som forklaringsvariabler. All slik sekundærbruk av data vil skje i samarbeide med forskerne som er ansvarlig for analysene (medforfatterskap etc). Slik bruk av data av andre TNS forskere vil også måtte godkjennes av styringsgruppen, som vil påse at bruk ikke er i konflikt andre delprosjekter.

Før innsendelse av manuskripter til publisering skal alle manuskripter godkjennes av styringsgruppen. Styringsgruppen vil påse at presentasjon av data er i tråd med TNS-studiens godkjennelser og protokoller. Styringsgruppen vil også sikre at dobbeltpublisering unngås, påse at presentasjon av sekundærdata ikke ødelegger for publikasjon av primærdata i andre delprosjekter, eller at publikasjoner med primærdata eller sekundærdata ødelegger for metodeartikler eller valideringsartikler. Forfatterskap ved alle artikler følger selvfølgelig vanlig praksis i vitenskapelige journaler og Vancouver regelverket.

Denne avtalen undertegnes i 2 eksemplarer hvorav styringsgruppen og delprosjektansvarlig beholder hver sitt eksemplar.

Godkjent styringsgruppen Typisk norsk-studien:

Dato:_____

Signatur:_____

Delprosjektansvarlig:

Dato:_____

Signatur:_____

The following pages contain a complete overview of samples, questionnaires and endpoints. The samples and datasets may already be dedicated to a sub-project, however, data may still be available for secondary use as described on page 2. Contact the "Steering group" (lead by Prof. Rune Blomhoff) to find out whether certain samples or datasets are available.

Biobank samples

Before surgery (invitation)

Citrate (2x4^{0}C)

- Plasma x 7 (Intermediate biomarkers of disease, cancer biomarkers)

Pax

RNA, miRNA, DNA isolation, Gene expression

DBS

Compliance biomarkers, Intermediate biomarkers of disease, cancer biomarkers.

Baseline, 6 mnths, 1yr

Citrate (1xRT, 1x 4^{0}C)

- Plasma x 7 (Intermediate biomarkers of disease, cancer biomarkers, heamostasis)
- Red blood cells x 2
- Buffy coat for PBMC isolation (DNA damage /repair)

EDTA (1x)

- Whole blood before spin x 3 (Comet assay , DNA isolation SNP analysis)
- Plasma x 5 (Intermediate biomarkers of disease, cancer biomarkers)
- Red blood cells x 2
- Buffy coat for PBMC isolation (Crosslinked DNA/histones for Chip-on-chip analysis)

Heparin

- Isolation of PBMC (Ex vivo stimulation)
- Plasma x 1 (Intermediate biomarkers of disease, cancer biomarkers)

Serum

- Serum x 6, before OGT (Intermediate biomarkers of disease, cancer biomarkers, cirk DNA?)
- Serum 1x after OGT (Intermediate biomarkers of disease, cancer biomarkers)

Pax

Before OGT (RNA, miRNA, DNA isolation,) Gene expression)

After OGT (RNA, miRNA, DNA isolation, Gene expression)

DBS

Compliance biomarkers, Intermediate biomarkers of disease, cancer biomarkers.

Questionnaires

Questionnaire	Information	Time-point during intervention
Registration form	Diabetes type I or II, insulin, Beta-blokkere, Metformin, Statines, blood pressure medicine, anticoagulant therapy (Marevan/Warfarin), Last week: AbylE, ibux, globoid, dispril, brexidol, aspirin, tran/ omega-3, dietary supplements	V2, V3, V4, V5,V6,V7, V8, V9
Background information	Social status, education, working status/sick leave, disability aid, family history of CRC or other type of cancer	V2
FFQ	Dietary habit last 12 months, in g/day. Servings/day (måltider). Gender, age, hight, weight, smoking status and amount of sigarettes/day	V1, V4, V5, V6, V7, V8, V9
SF-36	Quality of life, self-efficacy, physical function	V2, V3, V4, V5, V6, V7, V8, V9
Fatigue	Degree of tiredness, sleepy, energy-level, weakness, loss of memory	V2, V3, V4, V5, V6, V7, V8, V9
Physical activity	Times/week or day, intensity, duration each time, working time/leisure time, hours of sedentary per day Background information: Social status, education, working status/sick leave, disability aid etc.	V2, V3, V4, V5, V6, V7, V8, V9
Adherence to dietary guidelines/ Compliance questionnaire	Gender, age, height, weight, questions regarding dietary guidelines, physical activity (minutes/day, intensity per time)	V1, V2, V3, V4, V5, V6, V7, V8, V9
Comorbidity	Heart infarction, angina pectoris, heart failure, others heart disease, brain stroke, astma, chronic bronchitis, diabetes, eczema, other cancer, rheumatoid arthitis, Bekhterev's disease, osteoporosis, fibromyalgia, arthrosis	V2, V3, V4, V5, V6, V7, V8, V9
Weighed 7-day food diary	Grams/day all foods and drinks during whole day for 7 days in a row	Sub-group at V2 and V3

Process-evaluating qst	Patients give information about which intervention activity they have used and evaluates their experience	V3, V4
PG-SGA	Nutritional status, self-reported weight and weight-change last months, food intake last months, disease/treatment-related symptoms leading to reduced dietary intake, physical function	V2, V3, V4, V5, V6, V7, V8, V9

Preplaned endpoints

Outcomes	Instrument	V1 (Pre-surgery)	V2 (Base line)	V3 (6 mo)	V4 (12 mo)	V5 (3 yr)	V6 (5 yr)	V7 (7 yr)	V8 (10 yr)	V9 (15 yr)
Primary endpoints										
Mortality, cancer recurrence, comorbities, treatments, medical receipt	National health/death registries, registration form at visits, patient medical record	X	X	X	X	X	X	X	X	X
Self reported comorbidities	Questionnaire about comorbidity (cancer, CVD, diabetes, other inflammatory related diseases),		x	x	x	x	x	x	x	X
Adherence/Compliance to dietary recommendations, NFBDG (1 week last 2 months)	Compliance questionnaire	x	x	x	x	x	x	x	x	X
Secondary endpoints										
Quality of life	SF-36 questionnaire		x	x	x	x	x	x	x	X
Fatigue	Questionnaire about fatigue		x	x	x	x	x	x	x	X
Dietary pattern, energy intake (preceeding 12 months)	Food Frequency Questionnaire (FFQ)	x			x	x	x	x	x	X
Vitamin D status	Venous blood samples, and finger-prick blood sample	x	x	x	x	x	x	x	x	X
Dietary intake, energy consumption	Weighed 7-days food dairy		x	x						
Biomarkers food intake	Venous blood samples, finger-prick blood sample (DBS cards), urine samples	x	x	x	x	x	x	x	x	X
Dietary intake last day	24 h food recall (only group A)		x	x	x	x	x	x	x	X

Nutritional status	PG-SGA screening		x	x	x	x	x	x	x	X
Body composition-distribution of fat depot, sarcopenic obesity	Computertomography (CT)	x			x					
Body composition	BIA , DEXA, weight, height, hip/waist circumference		x	x	x	x	x	x	x	X
BMI, waist/hip-ratio	Weight, height, waist- and hip circumference	x	x	x	x	x	x	x	x	x
Blood pressure	Measurement of blood pressure under resting condition		x	x	x	x	x	x	x	x
Glucose/insulin regulation	Oral glucose tolerance test		x	x	x	x	x	x	x	x
Biomarkers of diseases and inflammation, haemostasis	Venous blood samples, and finger-prick blood sample (DBS cards)	x	x	x	x	x	x	x	x	x
Gene expression, DNA/SNP analysis, Cholesterol efflux, PBMC_DNA damage/repair	Venous blood samples, and finger-prick blood sample (DBS cards)	x	x	x	x	x	x	x	x	x
Gut microbiota in colon	Feces sample	x			x					x
Physical function, muscle strength	Handgrip strength, 6 minute walking test (6MWT), Sit-to-stand test, VO2 max-test treadmill	x	x	x	x	x	x	x	x	x
Total physical activity in minutes/METS intensity Energy expenditure, steps, inacitvity/sleeping in minutes	SenseWear Armband		x	x	x	x	x	x	x	x
Physical activity (PA)	Self-reported PA from questionnaire (based on HUNT3 study), compliance	x	x	x	x	x	x	x	x	x

	questionnaire									

Appendix C

Data access and publication policy POLARIS

DATA ACCESS AND PUBLICATION POLICY

POLARIS

(Predicting OptimaL cAncer RehabIlitation and Supportive care)

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Rationale

"To enable better research for improving personalized rehabilitation, collaboration between excellent research teams and sharing of data where and when possible and useful is of utmost importance. Alpe d'HuZes therefore strongly supports this POLARIS effort".
Peter Kapitein, Ambassador of Alpe d'HuZes/KWF fund

Numerous cancer rehabilitation and supportive care programs targeting quality of life (QoL) outcomes exist. These programs have been offered as home-based, clinical based or self-help programs and have generally focused on physical activity and exercise, and psychosocial functioning, e.g. cognitive behavioral therapy, psycho-education, and social and emotional support. Various randomized controlled trials have been conducted to evaluate physical activity/exercise and psychosocial interventions. However mean effect sizes of these programs on QoL outcomes are generally small to moderate. Explanations for the small to moderate effect sizes include problems with program participations, adherence and success, and the use of an one-size- fits-all approach to improve the QoL in a heterogeneous group of cancer patients. Therefore, physical activity/exercise and psychosocial interventions should be optimally tailored to the individual states, needs, preferences, capabilities and characteristics of a patient.
To be able to shift from an one-size-fits-all approach to tailored interventions, it is essential to know *what* existing program works for *whom*, and under *which* circumstances, i.e. to identify important moderators of intervention effect. Moderators identify which patients might be most responsive to the intervention, providing valuable information for decision making. To further improve physical activity/exercise and psychosocial interventions, more insight into the working *mechanisms* are needed, i.e. mediators of the intervention effect.

Aim

In the POLARIS study, we aim to:

1) Conduct an individual patient data (IPD) meta-analysis to evaluate the effectiveness of physical activity/exercise and psychosocial interventions on (health-related) QoL compared with a usual care, wait-list or attention control group in cancer patients and survivors;
2) Evaluate which socio-demographic, clinical and personal characteristics, and intervention type and circumstances moderate the effect of physical activity/exercise and psychosocial interventions on QoL of cancer patients;
3) Build and validate a clinical prediction model identifying the most relevant predictors of intervention success (i.e. improvement in QoL).

Funding

The POLARIS study is supported by the Alpe d'HuZes foundation/Dutch Cancer Society (grant number VU 2011-5045), via the "Bas Mulder Award" granted to L.M. Buffart.

Study Coordination

Coordination of the POLARIS study was performed at the EMGO+ Institute for Health and Care Research, one of the interfaculty research institutes of the VU University Medical Center Amsterdam and the VU University Amsterdam up to March 2020. Since then, the coordinating researcher moved to the Radboud University Medical Center in Nijmegen. Study coordinator is Dr. Laurien M. Buffart.

e-mail: Laurien.buffart@radboudumc.nl
phone: +31 24 36 13674

POLARIS consortium

All collaborators that have shared data with the POLARIS database form the POLARIS consortium.

Definitions

Collaborators:	All parties that are members of the POLARIS consortium.
PROVIDER:	Principal investigator of a research group providing data from the RCT for the POLARIS database, and who acts as consortium member.
Third Recipient:	A person/entity that uses the data from the POLARIS database for proposed analyses.

Data ownership and data confidentiality

- The data made available for the POLARIS database are and remain the property of the PROVIDER.
- All data that are included in the POLARIS database will be stored securely at the Radboudumc and are treated as confidential.
- All data in the POLARIS database are pseudonymized; all confidential and privacy sensitive information is removed, and the data is not traceable to patients.
- *PROVIDERs* may decline participation on a paper-by-paper basis, without giving any reason.
- *PROVIDERs* have to sign the Agreement on Data Sharing - PROVIDER before transferring their data to the POLARIS database.
- *PROVIDERs* have to confirm that they are authorized to provide the data to the POLARIS database.

Data access and use

Data from the POLARIS database can be used by PROVIDERs and third parties under the rules provided in his document.

- To access the POLARIS data, a paper proposal should be submitted in writing to the study coordinator (see paper proposal and publication rules).
- After receiving a paper proposal, the study coordinator will contact each *PROVIDER* to ask permission for the use of their data for the proposed study.
- Each *PROVIDER* will be given three weeks to decide whether he/she approves that the proposed analyses are conducted on the data they provided to the POLARIS database. A reminder will be send after two weeks.
- If the *PROVIDER* decides not to participate, his/her data will not be included in the

proposed analyses.

- The data in the POLARIS database can only be used for the proposed analyses, and is not allowed to be used for other studies nor should it be provided to third parties without written permission from each *PROVIDER*.
- The data can only be used according to the proposed analyses. In case other research questions are considered based on the same data base, approval for this new research question should be obtained.
- Access to the POLARIS data for consortium members is free of charge.
- POLARIS data is only available for non-commercial scientific research.
- *Third Recipients* will have to sign the Data Sharing Agreement-Third Recipient before they receive the data for analyses.

Paper proposals and publication rules

- Paper proposals should include information on authors, working title, the research question(s) to be addressed, the variables to be included, the analysis plan, the timetable and targeted journal(s) (see **Appendix B1, example in Appendix B2**).
- The Study coordinator will check potential overlap with other proposals or competing interests (i.e. ongoing studies using the POLARIS database). In case of conflicts of interest that cannot be resolved by the individuals involved, the issues at hand will be presented in writing to the Study coordinator, who will make the final decision, blind to the involved authors.
- In case the proposed research activities exceed the proposed timeline by six months or more, the topic will be made available to other researchers. Before exceeding the time line, the leading author may ask permission in writing of the Study coordinator to extend the proposed timeline.
- A leading (first) author can submit a maximum of two paper proposals at the same time. After the paper has been submitted to a journal, the author is allowed to submit the next research proposal. Paper proposals for PhD students, i.e. proposals for papers to be part of the PhD thesis, are an exception. For a PhD thesis, a PhD proposal (Appendix C1, example in Appendix C2) can be submitted including a maximum of 5 papers answering several research questions.
- The results of the analysis will be written down and submitted for publication in scientific peer-reviewed journals. The submitted version will be sent to all Providers.
- Before submission, the paper will be sent to the Study coordinator for information and approval to be submitted as a POLARIS paper. The Study coordinator has 2 weeks to check whether the paper is in correspondence with the paper proposal and that the acknowledgments (see acknowledgments) are used in a correct manner.
- The lead author (or corresponding author) is responsible for the quality of the paper.
- At the time of acceptance, the final paper and analyzed dataset and scripts should be sent to the Study coordinator.
- When the manuscript has been accepted for publication, the PDF of this paper will be e- mailed to each member of the POLARIS Consortium or a link to the open access journal will be published on the POLARIS website.

(co-) authorship

- For (co-)authorship, the POLARIS Consortium complies with the Vancouver Protocol, i.e. authorship credit should be based on (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; (2) drafting the article or

revising it critically for important intellectual content; and (3) final approval of the version to be published.

- In all publications, the POLARIS Consortium will be mentioned as a co-author, i.e. '(on behalf of) the POLARIS Consortium'.
- The participating studies and investigators of the POLARIS Consortium will be listed at the end of each publication, with a maximum of 2 investigators per study (PI and co-PI).
- Names of lead authors conducting the analysis and writing the paper will be listed separately in addition to the POLARIS Consortium.

Information and communication

- Contact the POLARIS coordinator for all questions regarding the POLARIS.
- New information will be communicated through digital newsletters.
- Information on the POLARIS study can also be found on the website of POLARIS; www.polaris-study.org.

Acknowledgments

All reports on the POLARIS study should include the following statement in the acknowledgments:

The POLARIS study is supported by the Alpe d'HuZes foundation/Dutch Cancer Society (grant number VU 2011-5045), via the "Bas Mulder Award" granted to L.M. Buffart.

The authors thank all the patients who took part in the trials, and the collaborating investigators that kindly supplied their trial data.

POLARIS coordinator: LM Buffart.

POLARIS PROVIDERs: name PROVIDER + trial presented in Appendix A

Appendix A1: Overview Exercise trials included in POLARIS

Table 1. Exercise trials and contact persons (Dec 2020)

Exercise Trial publication	PI (contact person)	Country	Study Acronym
Arbane et al. Lung Cancer 2011;71:229-34	Gill Arbane	UK	
Cadmus et al. Psychooncology 2009;18:343-52	Melinda Irwin	USA	IMPACT
Cormie et al. BJU Int 2015;115:256-66	EMRI[1]	AUS	
Courneya et al. Eur J Cancer Care 2003;12:347-57	Kerry Courneya	CAN	CANHOPE
Courneya et al. JCO 2003;21:1660-8	Kerry Courneya	CAN	REHAB
Courneya et al. JCO 2007;25:4396-404	Kerry Courneya	CAN	START
Courneya et al. JCO 2009;27:4605-12	Kerry Courneya	CAN	HELP
Daley et al. JCO 2007;25:171-21	Amanda Daley	UK	
Duijts et al. JCO 2012;30:4124-33	Neil Aaronson	NL	EVA
Galvão et al. JCO 2010;28:340-7	EMRI[1]	AUS	
Galvão et al. Eur Urol 2014;65:856-64	EMRI[1]	AUS	RADAR-exercise
Goedendorp et al. Oncologist 2010;15:1122-32	Hans Knoop, Martine Goedendorp	NL	
Griffith et al. Cancer 2009;115:4874-84	Jennifer Wenzel	USA	
Hayes et al. Breast Cancer Res Treat 2013;137:175-86	Sandi Hayes	AUS	Exercise for Health
Herrero et al. Int J Sports Med 2006;27:573-80	Alejandro Lucia	Spain	
Irwin et al. Cancer Epidemiol Biomark Prev 2009;18:306-13,	Melinda Irwin	USA	YES
Kampshoff et al. BMC Med 2015;13:275	Laurien Buffart	NL	REACT
Korstjens et al. Psychosom Med 2008;70:422-9	Anne May	NL	OncoRev
Mehnert et al. Onkologie 2011;34:248-53	Anja Mehnert	GER	
Mutrie et al. BMJ 2007;334-517	Nannette Mutrie	UK	
Taaffe et al. Eur Eurol 2017;72:293-299	EMRI[1]	AUS	
Ohira et al. Cancer 2006; 106: 2076-83	Katie Schmitz	USA	WTBS
Persoon et al. PLoS ONE 2015	Laurien Buffart	NL	EXIST
Schmidt et al. Int J Cancer 2015; 137:471-80	Karen Steindorf	GER	BEATE
Short et al. Psychooncology 2015;24:771-8	Camille Short	AUS	MM4L
Speck et al. Breast Cancer Res Treat 2010;121:421-30	Katie Schmitz	USA	PAL
Steindorf et al. Ann Oncol 2014;25:2237-43	Karen Steindorf	GER	BEST
Thorsen et al. JCO 2005;23:2378-88	Lene Thorsen	NOR	
Travier et al. BMC Med 2015;13:121. van Vulpen et al. MSSE 2016;48:767-75	Anne May	NL	PACT
Van Waart et al. JCO 2015;33:1918-27 Van Waart et al. Int J Colorectal Dis 2018;33:29-40	Neil Aaronson, Martijn Stuiver	NL	PACES
Winters-Stone et al. J Cancer Surv 2012;6:189-99	Kerri Winters-Stone	USA	
Winters-Stone et al. Osteoporosis Int 2013;24:1637-46	Kerri Winters-Stone	USA	
Winters-Stone et al. Arch Phys Med Rehabil 2015;96:7-14	Kerri Winters-Stone	USA	
Wiskemann et al. Blood 2011;117-2604-13.	Joachim Wiskemann	GER	

[1]EMRI=Exercise Medicine Research Institute: Rob Newton, Daniel Galvão, Dennis Taaffe

Appendix A2: Overview PSI trials included in POLARIS

Table 2. Trials on Psychosocial interventions (PSI) and contact persons (Dec 2020)

PSI Trial publication	PI (contact person)	Country	Study Acronym
Armes et al. Cancer 2007; 110: 1385-95	Jo Armes	UK	
Arving et al. Cancer Nurs 2007; 30: E10-19	Birgitta Johansson, Cecilia Arving[a]	SWE	
Braamse et al. Ann Hematol 2016;95:105-14	Joost Dekker	NL	
Chambers et al. Psychooncol 2013; 22:1025-34	Suzanne Chambers	AUS	
Duijts et al. JCO 2012; 30:4124-33	Neil Aaronson	NL	EVA
Ell et al. JCO 2008;26:4488-96	Kathleen Ell	USA	ADAPt-C
Ferguson et al. Psychooncology 2012; 21:176-186	Robert Ferguson	USA	MAAT
Gellaitry et al. Psychooncology 2010; 19:77-87	Robert Horne	UK	
Gielissen et al. JCO 2006; 24:4882-7	Marieke Gielissen, Hans Knoop	NL	
Goedendorp et al. Oncologist 2010; 15:1122-32	Hans Knoop, Martine Goedendorp	NL	
Graves et al. Palliat Support Care 2003; 1:121-134	Kristi Graves	USA	
Heiney et al. Cancer Nurs 2003; 26:439-447	Sue Heiney	USA	
Johansson et al. Br J Cancer 2008;99:1875-1983	Birgitta Johansson [a]	SWE	
Kimman et al. Eur J Cancer 2011; 47:1027-1036	Liesbeth Boersma, Merel Kimman	NL	
Mann et al. Lancet Oncol 2012;13:309-318	Myra Hunter	UK	MENOS 1
Meneses et al. Oncol Nurs Forum 2007;34:1007-16	Karen Meneses	USA	
Northouse et al. Psychooncology 2005;14:478-491	Laura Northouse	USA	FOCUS
Northouse et al. Cancer 2007; 110:2809-18	Laura Northouse	USA	
Northouse et al. Psychooncology 2013;22:555-63	Laura Northouse	USA	
Savard et al. JCO 2005; 23:6083-96	José Savard	CAN	
Savard et al. Pall Support Care 2006; 4:219-237	José Savard	CAN	
van den Berg et al. JCO 2015;33:2763-71	Judith Prins	NL	BREATH

[a] Yvonne Brandberg, Bengt Glimelius

Appendix B1: Proposal scientific publication POLARIS

Proposal scientific publication POLARIS (max. 2 A4)

Date of submission:	Date of approval:

1. Working title
2. Name and affiliation of first/lead author
3. Suggested co-author(s)
4. Email address for correspondence
5. Rationale
6. Research question(s)
7. Variables to be used
   (outcomes, patient population, time points etc)
8. Method of analyses
9. Time schedule
10. Proposed journal

Appendix B2: Example proposal scientific publication POLARIS

1. **Working title**
   Effectiveness of exercise interventions on health-related quality of life. A meta-analysis on individual patient data.

2. **Name and affiliation of first/lead author**
   Laurien M Buffart
   EMGO Institute for Health and Care Research and the VU University Medical Center, department of Epidemiology and Biostatistics.

3. **Suggested co-author(s)**
   J. Kalter, J. Brug, R.U. Newton, K.S. Courneya, M. Chin A Paw

4. **Email address for correspondence**
   l.buffart@vumc.nl

5. **Rationale**
   Optimizing quality of life (QoL) for cancer patients during and after primary cancer treatment requires evidence-based rehabilitation and supportive care. Numerous rehabilitation and supportive care programs aiming at improving QoL are available. These programs focus on exercise and psychosocial function, and generally use a one-size fits all approach. However, clinical practice shows that these programs may be effective in some patients but not in others. Various RCTs have been conducted to evaluate these programs, with a main emphasis on exercise and psychosocial support. However, mean effect sizes of the rehabilitation and supportive care programs on QoL outcomes were generally small to moderate. Explanations for small to moderate effects include problems with program participation, adherence and success, and the use of one-size fits all-approaches to improve QoL in a heterogeneous group of cancer patients. Since every cancer patient is unique, care should be tailored to the individual needs, preferences, capabilities and characteristics of each patient. The Predicting OptimaL cAncer RehabIlitation and Supportive care (POLARIS) study aims to determine what rehabilitation and supportive care program works best for whom, under what circumstances, and through which mechanisms. In addition, to stimulate active participation of clinicians and patients making the most optimal choice for rehabilitation and supportive care programs, a clinical decision rule will be built and implemented. This paper focuses on the first step, i.e. evaluation of the effectiveness of physical activity and exercise interventions on QoL in cancer patients and survivors, based on a meta-analysis of individual patient data from existing RCTs.

6. **Research question(s)**
   What is the effectiveness of physical activity and exercise interventions on (health-related) quality of life compared with usual care or wait-list control group in cancer patients and survivors.

7. Variables to be used

- Outcomes: Quality of life, sociodemographic characteristics (age, gender, education), clinical characteristics (type of treatment, length of treatment, confidence in treatment, presence of co-morbidities, performance status), intervention characteristics (mode, duration, intensity, frequency, supervision).
- Patient population: all diagnosis
- Time points: pre-and post- intervention values, of physical activity/interventions during and after cancer treatment.

8. Method of analyses

The primary outcome of the study is (health-related) QoL at the end of the intervention. Other variables that will be used in the statistical analysis are baseline Qol, cancer diagnosis, cancer stage, time since diagnosis when starting the intervention, gender, age at baseline, education level at baseline, intervention mode (e.g. resistance, endurance), intervention duration, exercise intensity, exercise frequency, exercise session duration, exercise supervision (i.e. yes/no), treatment type (e.g. radiotherapy), length of treatment, confidence in treatment, performance status (e.g. Karnofsky Performance Scale), and presence of co morbidities. Multilevel regression analyses will be used to evaluate the effect of physical activity/exercise interventions on QoL.

9. Time schedule

Data analysis and drafting the article 01-01-2014 to 31-03-2014.
Submission, after collaborators meeting (mid 2014).

10. Proposed journal

Journal of Clinical Oncology

Appendix C1: Proposal PhD thesis POLARIS

Date of submission:	Date of approval:

1. Working title thesis
2. Name PhD candidate(s) and affiliation
3. Names promoter(s), co-promotor(s) and affiliation
4. Rationale
5. Research questions (5)
6. Method of analyses
7. Time schedule

1. **Working title thesis**

POLARIS: Predicting OptimaL cAncer RehabIlitation and Supportive Care. A meta-analysis of individual patient data.

2. **Name PhD candidate(s) and affiliation**

Joeri Kalter

VU University Medical Center, department of Epidemiology & Biostatistics and the EMGO Institute for Health and Care Research, Amsterdam, the Netherlands

3. **Names promoter(s), co-promotor(s) and affiliation**

Promotors:

- Prof. dr. J. Brug, VU University Medical Center, Amsterdam, The Netherlands
- Prof. dr. I.M. Verdonck-de Leeuw, VU University Medical Center Amsterdam, The Netherlands

Co-promotor:

- Dr. L. Buffart, VU University Medical Center, Amsterdam, The Netherlands

4. **Rationale**

Optimizing quality of life (QoL) for cancer patients during and after primary cancer treatment requires evidence-based rehabilitation and supportive care. Numerous rehabilitation and supportive care programs aiming at improving QoL are available. These programs focus on exercise and psychosocial function, and generally use a one-size fits all approach. Since every cancer patient is unique, care should be tailored to the individual needs, preferences, capabilities and characteristics of each patient. It should integrate soma and psyche, address the patients' autonomy, and should be provided in an efficient way. The Predicting OptimaL cAncer RehabIlitation and Supportive care (POLARIS) study aims to determine what rehabilitation and supportive care program works best for whom, under what circumstances, and through which mechanisms. In addition, to stimulate active participation of clinicians and patients making the most optimal choice for rehabilitation and supportive care programs, a clinical decision rule will be built and implemented.

5. **Research questions (5)**

1) What is the effectiveness of psychosocial interventions on (health-related) quality of life compared with usual care or wait-list control group in cancer patients and survivors.
2) Which socio-demographic and clinical characteristics moderate the effect of psychosocial interventions on quality of life of cancer patients and survivors.
3) Which socio-demographic and clinical characteristics moderate the effect of physical activity and exercise interventions on quality of life of cancer patients and survivors.
4) Which psychosocial characteristics moderate the effect of psychosocial interventions on quality of life of cancer patients and survivors.
5) What is the predictive value of socio-demographic characteristics, clinical characteristics, personal characteristics, and circumstances for improvement in quality of life after cancer rehabilitation and supportive care.

6. Method of analyses

Example research question 1: Effectiveness of psychosocial interventions on health-related QoL

The primary outcome of the study is (health-related) QoL at the end of the intervention. Other variables that will be used in the statistical analysis are baseline QoL, cancer diagnosis, cancer stage, time since diagnosis when starting the intervention, gender, age at baseline, education level at baseline, intervention type (e.g. cognitive behavioral therapy), intervention format (e.g. group, individual, couples), intervention duration, number of care providers involved in the intervention, total number of sessions of the intervention, treatment type (e.g. radiotherapy), duration of treatment, confidence in treatment, performance status (e.g. Karnofsky Performance Scale), and presence of co morbidities. Multilevel regression analyses will be used to evaluate the effect of psychosocial interventions on QoL.

7. Time schedule

	Start	**End**
Preparation of the study	01-01-2012	30-09-2012
Data collection	01-10-2012	31-12-2013
Analysis and writing article 1	01-01-2014	31-03-2014
Analysis and writing article 2	01-04-2014	31-07-2014
Analysis and writing article 3	01-08-2014	31-12-2014
Analysis and writing article 4	01-01-2015	31-03-2015
Analysis and writing article 5	01-04-2015	31-07-2015

Appendix D: POLARIS Data Sharing Agreement - PROVIDER

AREEMENT ON THE SHARING OF
PSEUDONYMIZED PERSONAL DATA – POLARIS
(Predicting OptimaL cAncer Rehabilitation and Supportive care)

A20- xxxx

This agreement (hereinafter referred to as "Agreement") is made and entered by and between:

<entity name, address >, legally represented by **< name >** (the undersigned), hereinafter referred to as "PROVIDER"

and

Stichting Radboud Universitair Medisch Centrum established at Geert Grooteplein 10, P.O. Box 9101, 6500 HB Nijmegen, the Netherlands, represented by its legal representative, J. Sjoerts, hereinafter referred to as "RECIPIENT";

PROVIDER and RECIPIENT hereinafter jointly referred to as "Parties" and individually as "Party";

WHEREAS

a. PROVIDER has obtained and / or generated DATA as further defined below;
b. RECIPIENT, through **L.M. Buffart,** hereinafter referred to as "RECIPIENT SCIENTIST", has requested PROVIDER, through **< name provider >**, hereinafter referred to as "PROVIDER'S SCIENTIST", to provide RECIPIENT with the DATA for use by RECIPIENT'S SCIENTIST for the purpose of the individual patient data meta-analyses proposed in the POLARIS study.
Registry: PROSPERO 2013 CRD42013003805 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42013003805, and
Protocol paper: Buffart et al. Syst Rev 2013;2:70.
Available from: https://pubmed.ncbi.nlm.nih.gov/24034173/
c. The purpose and means of the POLARIS study have been determined by RECIPIENT;
d. PROVIDER is willing, subject to the terms and conditions of this Agreement, to provide the DATA to RECIPIENT.
e. PROVIDER agrees to the POLARIS policy document (annex III) in which among others an access policy is established to further distribute the DATA to academic partners (Third Recipients).

I Definitions

1. DATA: the data being transferred under this Agreement is the data that is further specified in Annex I to this Agreement, provided without directly identifying personal information. The DATA constitutes pseudonymized personal health data under the GDPR.
2. RECIPIENT'S RESEARCH PLAN: The research plan specified in Annex II to this Agreement for which the DATA may be used.
3. EFFECTIVE DATE: The date of last signing of this Agreement.
4. INVENTION: any invention, discovery , improvement, material, signal, process, formula, know-how or other innovation related to or arising from the use of the DATA and/or CONFIDENTIAL INFORMATION, whether patentable or not and obtained as a result of the performance of RECIPIENT'S RESEARCH PLAN.
5. CONFIDENTIAL INFORMATION: All information, know-how, grant applications, method of work, techniques, expertise of PROVIDER regarding the DATA, its characteristics and PROVIDER's research concerning the DATA, whether of a scientific, technical, engineering, operational, or

economic nature, supplied to or obtained by RECIPIENT in written form, in the form of drawings or in the recording of oral conversation, or samples.

6. GDPR: the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation)
7. APPLICABLE DATA PROTECTION LAW*:* the GDPR and any additional locally applicable data protection legislation.
8. SUBJECT(S): shall mean the patient or other person from whom the DATA was obtained.
9. ANALYSIS: proposed analysis based on the data from the POLARIS database
10. STUDY COORDINATOR: dr. L.M. Buffart coordinates the POLARIS study, supported by PhD students from her research group.
11. THIRD RECIPIENT: a person/entity that uses the data from the POLARIS database for proposed analyses after signing the Third Recipient-version of the DTA to acquire the data as described in the POLARIS policy document.

II. Terms and Conditions of this Agreement:

1. The DATA and any other information provided is made available as a service to the research community and no ownership rights in the DATA and any other information shall be obtained by RECIPIENT under this Agreement.

2.

a. DATA shall be provided by PROVIDER in a sufficiently secure manner and Parties shall handle all DATA in accordance with the APPLICABLE DATA PROTECTION LAW and shall keep such DATA confidential without any of the exclusions contained in Article 11 below.
b. With respect to the DATA, RECIPIENT shall be considered to be a separate data controller under the APPLICABLE DATA PROTECTION LAW for the processing of the DATA for RECIPIENT'S RESEARCH PLAN.
c. RECIPIENT shall implement appropriate technical and organizational measures to meet the requirements for data controllers of the APPLICABLE DATA PROTECTION LAW.
d. If RECIPIENT becomes aware of a personal data breach, RECIPIENT shall promptly notify PROVIDER. In such a case Parties will fully cooperate with each other to remedy the personal data breach, fulfill the statutory notification obligations timely and cure any damages. The term 'personal data breach' refers to articles 33 and 34 of GDPR.
e. In the event that SUBJECT withdraws his/her permission for the use thereof, PROVIDER shall supply RECIPIENT with sufficient information and RECIPIENT shall immediately cease all use of the relevant DATA and shall delete all copies of the relevant DATA. Upon request from PROVIDER, RECIPIENT shall confirm in writing the complete deletion of such DATA.
f. PROVIDER shall be data controller of the DATA under the GDPR up until the moment the DATA is provided to RECIPIENT.

The Parties' contact details for inquiries regarding handling and protection of DATA are as follows:

For RECIPIENT, to:

RvB / Bestuurlijke en Juridische zaken / Privacy office
Postbus 9101 (route 632), 6500 HB Nijmegen
Geert Grooteplein Zuid 10 / Looproute 526
E-mail: privacy@radboudumc.nl
Phone number privacy office: 024-3616378 or internal number 16378

For PROVIDER, to:
Name: ……..

Address: …….
e-mail:……..

3. RECIPIENT shall not carry out any procedures with the DATA, such as linking, comparison, processing, with which the identity of the Subject could be derived. The RECIPIENT and the RECIPIENT SCIENTIST agree that the DATA:
   (a) is to be used only for the academic purposes as described in RECIPIENT'S RESEARCH PLAN and the POLARIS policy document (annex III);
   (b) will not be used for other, including commercial purposes.

   Furthermore, in carrying out the RECIPIENT'S RESEARCH PLAN, RECIPIENT shall not allow third parties that are not expressly mentioned in the Annexes to access or otherwise process the DATA without prior written approval of PROVIDER.

   However, as an exception to the foregoing, such prior approval shall not be required for service providers in the context of the standard business operations of RECIPIENT, such as parties who supply ICT infrastructure maintenance. RECIPIENT will safeguard that any data processors who have access to the DATA are instructed by a binding agreement to process the personal data in accordance with the requirements stated in the GDPR.

4. Except as provided in this Agreement, no express or implied licenses or other rights are provided to the RECIPIENT under any Intellectual Property (IP) rights of PROVIDER.

5. The DATA will be provided at no cost.

6. PROVIDER acknowledges that it has read and consents to the access policy as set out in the POLARIS policy document (annex III) and thus that RUMC is permitted to send the DATA to third parties according to the following clauses:

   a. Upon receiving a proposal for an ANALYSIS from a Third Recipient, the STUDY COORDINATOR will contact the PROVIDER to ask permission for the use of the DATA for the proposed ANALYSIS.
   b. The PROVIDER is entitled to decline inclusion of the DATA on a case-by-case basis, without giving any reason, as established in article 3 of this agreement. PROVIDER will be given three weeks to decide whether he/she approves the ANALYSIS. A reminder will be sent after two weeks.
   c. In the event that PROVIDER wishes to withdraw the DATA from the POLARIS database, a written request shall be sent to and duly accepted by the STUDY COORDINATOR. RUMC will use its best efforts to contact any third parties that have already received the DATA based on the POLARIS policy document.
   d. Access to the DATA for consortium members is free of charge. The consortium members are identified in the POLARIS policy document. The STUDY COORDINATOR is entitled to impose a fee for the access of DATA to non-consortium members.

7. DATA will be provided to the RECIPIENT by PROVIDER's SCIENTIST in a sufficiently secure manner and in a format to be agreed upon by the RECIPIENT SCIENTIST and the PROVIDER's SCIENTIST.

8. PROVIDER warrants a) that it has verified that there is an appropriate legal ground for the provision of the DATA to RECIPIENT in accordance with the GDPR (such as Article 6 and/or 5.1 sub b GDPR) b) that there is a valid exception to the prohibition for processing personal health data (Article 9 GDPR) and c) that it shall be provided under approval from the relevant ethics committee

to the extent required. Apart from this, it is expressly understood that PROVIDER does not make any warranties regarding the DATA and specifically does not warrant or guarantee that the DATA will be accurate, be merchantable or useful for any particular purpose. PROVIDER cannot and shall not be held liable for any claims or damages by RECIPIENT or any third party, in connection with or as a result of the use of DATA by RECIPIENT. Unless and to the extent caused by PROVIDER's gross negligence or willful misconduct, RECIPIENT undertakes to hold harmless PROVIDER at all times against all of such damages or claims.

In regards to the DATA and personal data breaches, RECIPIENT shall be responsible and liable for any damages, losses and fines resulting from its own actions or failures to adhere to the terms of this Agreement and APPLICABLE DATA PROTECTION LAW and RECIPIENT shall indemnify and hold harmless PROVIDER for any of such damages. For the purposes of this sub clause, actions or omissions of data processors contracted by RECIPIENT, shall be attributed to RECIPIENT.

9. RECIPIENT agrees in its use of the DATA to comply with all applicable international and national laws, statutes, regulations and guidelines.

10. RECIPIENT shall treat all CONFIDENTIAL INFORMATION as confidential for the duration of this Agreement including any extension thereof and thereafter for a period of five (5) years following termination or expiry of this Agreement. Excluded from this obligation of confidentiality shall be any CONFIDENTIAL INFORMATION of which the RECIPIENT can reasonably demonstrate that it (a) was previously known to RECIPIENT, or (b) is, and/or becomes, publicly available during said five (5) year period through no fault of RECIPIENT, or (c) is independently and lawfully developed by the RECIPIENT, or (d) was published or otherwise disseminated in accordance with the publication procedure set out below in article 12. However, the foregoing exceptions shall not apply to: (a) CONFIDENTIAL INFORMATION contained within more general information that may fall within one or more of the exceptions, or (b) any combination of features or items of CONFIDENTIAL INFORMATION where one or more of the relevant individual features or items (but not the combination itself) may fall within one or more of the exceptions. The obligation of confidentiality shall not apply to any disclosure required by law, provided that RECIPIENT shall notify PROVIDER of any disclosure required by law in sufficient time so that PROVIDER may contest such requirement, if PROVIDER so chooses.

11. Parties acknowledge the importance of disseminating the results of the RECIPIENT'S RESEARCH PROJECT. Therefore, RECIPIENT shall endeavor to publish or otherwise publicly disclose information, any data, results or information generated using the DATA ("Disclosure(s)"), after review by PROVIDER. The following shall apply to Disclosures:
    a. Authorship of any publications shall follow the principles set out in the ICMJE recommendations 'Defining the Role of Authors and Contributors' as can be found on http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html .
    b. At least thirty (30) days before RECIPIENT submits a paper or abstract for Disclosure, RECIPIENT shall provide such paper or abstract to PROVIDER, who will have thirty (30) days to review proposed manuscripts and fifteen (15) days to review proposed abstracts to assure that its CONFIDENTIAL INFORMATION is protected. It is agreed that RECIPIENT will fully comply with any reasonable written request by PROVIDER to omit specified CONFIDENTIAL INFORMATION of PROVIDER from such paper, abstract, press release or other disclosure prior to Disclosure.
    c. In every Disclosure by RECIPIENT based upon results obtained from the research through the help of the received DATA provided by PROVIDER, RECIPIENT shall appropriately acknowledge PROVIDER and PROVIDER'S SCIENTIST as contributor of the DATA.

12. This Agreement will become effective on the EFFECTIVE DATE. Any clauses which will be expected or intended by its nature to survive the termination or the expiration of this Agreement, shall survive the termination or the expiration of this Agreement.

    Upon termination of this Agreement, the right to use the DATA and CONFIDENTIAL INFORMATION will automatically end.

13. This Agreement will be construed, governed, interpreted and enforced according to the laws of the Netherlands. Parties will first strive to settle any disputes amicably before taking legal action. All disputes arising out of or in relation to this Agreement that cannot be settled amicably will be brought before the competent court in the Netherlands, in the district in which the Provider resides.

14. This Agreement will be binding upon and inure to the benefit of the respective successors and assignees of the Parties hereto. However, RECIPIENT may not assign this Agreement in whole or in part without the prior written consent of the PROVIDER.

15. This Agreement may only be altered or amended by an instrument in writing signed by all of the Parties.

16. If any portion of this Agreement is in violation of any applicable regulation, or is unenforceable or void for any reason whatsoever, such portion will be inoperative and the remainder of this Agreement will be binding upon the Parties.

17. Both Parties acknowledge that the signatories to this Agreement are authorized representatives of each of the Parties and legally authorized to sign this Agreement.

18. If the lawful performance of any part of this Agreement by a Party is rendered impossible by or as a result of any cause beyond such Party's reasonable control, such Party will not be considered in breach hereof as a result of failing so to perform.

IN WITNESS WHEREOF, the Parties have executed this Agreement, in duplicate originals or as a signed PDF, as of the Effective Date.

For the **PROVIDER**

By:___ _____
Name:
Title
Date:_____

By:_____
Name: ……..
Title:…….
Date:_____

READ AND ACKNOWLEDGED:

_____
NAME
PROVIDER'S SCIENTIST

For **RECIPIENT**,

By:_____
Name: J. Sjoerts
Title: Director Tech Transfer Office, Radboudumc
Date:_____

By:_____
Name: prof. R. Bindels
Title: Head of the Dept. of Physiology, Radboudumc
Date:_____

READ AND ACKNOWLEDGED:

_____
Dr. L. M. Buffart
RECIPIENT'S SCIENTIST

ANNEX I

Description of the DATA, methods of transfer and storage, allowed processors

Data subjects The personal data transferred concern the following categories of data subjects:	Patients with cancer
Purpose of the transfer(s) The transfer is made for the following purpose:	See Annex II
Categories of data The personal data transferred concern the following categories (types) of data:	Health data NB: All health information qualifies as sensitive data as meant in the field below
Sensitive data (if appropriate) e.g.: • racial or ethnic origin, • political opinions, • religious or philosophical beliefs, • trade union membership, • genetic data, biometric data, • health data, • sex life and sexual orientation	Health related data. Among others: sex, height weight, cancer type and treamtent.
Method of transfer e.g.: Soft- or hardware encrypted USB drive, database entry such as in Castor, etc.	Secure transfer of data. Data can be supplied in any format (SPSS, STATA, SAS, etc.)
Method of data storage and security measures (e.g. method of encoding)	Secured network of Radboudumc
Authorized processors, if applicable, as indicated in clause 3 of the Agreement	NOT APPLICABLE

ANNEX II

Recipient's research plan

The purpose of the individual patient data meta-analyses proposed in the POLARIS study is described in the International prospective register of systematic reviews (PROSPERO).
PROSPERO 2013 CRD42013003805
Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42013003805.

The study protocol is published in an international peer-reviewed journal:
Buffart et al. Syst Rev 2013;2:70
Available from: https://pubmed.ncbi.nlm.nih.gov/24034173/

Appendix E: POLARIS Data Sharing Agreement – THIRD RECIPIENT

ACQUIRING
PSEUDONYMIZED PERSONAL DATA – POLARIS
(Predicting Optimal cAncer Rehabilitation and Supportive care)

A20-xxxx

This agreement (hereinafter referred to as "Agreement") is made and entered by and between:

Stichting Radboud Universitair Medisch Centrum established at Geert Grooteplein 10, P.O. Box 9101, 6500 HB Nijmegen, the Netherlands, represented by its legal representative, J. Sjoerts, hereinafter referred to as "RUMC";

and

<…>, established at , **other** >, represented by its legal representative <…>, hereinafter referred to as "Third Recipient".

Hereinafter jointly referred to as "Parties" and individually as "Party";

WHEREAS

a) RUMC has obtained data from Providers in the POLARIS database("DATA")
b) THIRD RECIPIENT, through **<…>**, hereinafter referred to as "THIRD RECIPIENT SCIENTIST", has requested RUMC, through **<…>**, hereinafter referred to as "RUMC'S SCIENTIST", to provide THIRD RECIPIENT with the DATA for use by THIRD RECIPIENT'S SCIENTIST for the purpose of its RESEARCH PLAN
c) The purpose and means of the RESEARCH PLAN have been determined by THIRD RECIPIENT;
d) RUMC is willing, subject to the terms and conditions of this Agreement and the POLARIS policy document, to provide the DATA to THIRD RECIPIENT.
e) The POLARIS policy document is an integral part of this Agreement and has been provided to Third Recipient.

I Definitions

1. DATA: the data being transferred under this Agreement is the data that is further specified in Annex I to this Agreement, provided without directly identifying personal information. The DATA constitutes pseudonymized personal health data under the GDPR.
2. RESEARCH PLAN: The research plan specified in Annex II to this Agreement for which the DATA will be used.
3. EFFECTIVE DATE: The date of last signing of this Agreement.
4. INVENTION: any invention, discovery , improvement, material, signal, process, formula, know-how or other innovation related to or arising from the use of the DATA and/or CONFIDENTIAL INFORMATION , whether patentable or not and obtained as a result of the performance of the RESEARCH PLAN.
5. CONFIDENTIAL INFORMATION: All information, know-how, data and experience of RUMC regarding the DATA, its characteristics, RUMC's research concerning the DATA, whether of a scientific, technical, engineering, operational, or economic nature, supplied to or obtained by THIRD RECIPIENT in written form, in the form of drawings or in the recording of oral conversation, or samples, which is reasonably required by THIRD RECIPIENT for performance

of RESEARCH PLAN.

6. GDPR: the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation)

II. Terms and Conditions of this Agreement:

1. The DATA and any other information provided is made available as a service to the research community and no ownership rights in the DATA and any other information shall be obtained by THIRD RECIPIENT under this Agreement.

2. a) Parties shall handle all DATA in accordance with the GDPR and any applicable local implementing legislation (hereinafter: "Applicable Data Protection Law").
b) With respect to the DATA, THIRD RECIPIENT shall be considered to be a separate data controller under the GDPR for the processing of the DATA for its RESEARCH PLAN.
c) THIRD RECIPIENT shall implement appropriate technical and organizational measures to meet the requirements for data controllers of the Applicable Data Protection Law.
d) If THIRD RECIPIENT becomes aware of a personal data breach, THIRD RECIPIENT shall promptly notify RUMC. In such a case Parties will fully cooperate with each other to remedy the personal data breach, fulfill the (statutory) notification obligations timely and cure any damages. A personal data breach refers to: 1) a personal data breach as meant in article 34a of the Dutch Data Protection Act, and 2) as of 25 May 2018, a personal data breach as meant in articles 33 and 34 of the European General Data Protection Regulation.
e) In the event that a person from whom DATA was obtained, withdraws his/her informed consent for the use thereof, RUMC shall supply THIRD RECIPIENT with sufficient information and THIRD RECIPIENT shall immediately cease all use of the relevant DATA and shall delete all copies of the relevant DATA. Upon request from RUMC, THIRD RECIPIENT shall confirm in writing the complete deletion of such DATA.
f) RUMC shall be data controller of the DATA under the GDPR up until the moment the DATA is provided to THIRD RECIPIENT.

3. The THIRD RECIPIENT and the THIRD RECIPIENT SCIENTIST agree that the DATA: (a) is to be used only for the academic purposes as described in the RESEARCH PLAN; (b) will not be used for commercial purposes and (c) will not be transferred to a third party. THIRD RECIPIENT shall not carry out the RESEARCH PLAN with any third party or entity without prior written approval of RUMC. THIRD RECIPIENT shall not attempt in any way to obtain the identity of the people to which the DATA relates.

4. THIRD RECIPIENT'S SCIENTIST shall keep RUMC'S SCIENTIST informed of the RESULTS arising from the RESEARCH PLAN and when requested shall provide an update of such RESULTS. Within thirty (30) days after the completion of the RESEARCH PLAN or the expiration or earlier termination of this Agreement, whichever occurs earlier, THIRD RECIPIENT shall provide RUMC with a written description of all research activities, analyses, tests or studies performed using the DATA (collectively, the "RESULTS").

5. THIRD RECIPIENT will report any INVENTIONS to RUMC and RUMC'S SCIENTIST. THIRD RECIPIENT shall promptly provide RUMC with a detailed written description of the INVENTION and indicate the role, if any, of any of THIRD RECIPIENT's employees in creating the INVENTION. Inventorship will be determined by applicable law. In the event the INVENTION is a joint INVENTION, both Parties shall make appropriate mutual arrangements concerning the protection and exploitation of such joint INVENTION.

6. Except as provided in this agreement, no express or implied licenses or other rights are provided to the THIRD RECIPIENT under any Intellectual Property (IP) rights of RUMC.

7. The DATA will be provided at no cost or with an optional transmittal fee solely to reimburse RUMC for the preparation. If a fee is requested, the amount will be indicated here:
<…>

8. DATA will be provided to the THIRD RECIPIENT by RUMC's SCIENTIST in a format to be agreed upon by the THIRD RECIPIENT SCIENTIST and the RUMC's SCIENTIST.

9. RUMC warrants a) that it has verified that there is an appropriate legal ground for the provision of the DATA to THIRD RECIPIENT in accordance with the GDPR (such as Article 6 and/or 5.1 sub b GDPR) b) that there is a valid exception to the prohibition for processing personal health data (Article 9 GDPR) and c) that it is provided under approval from the relevant ethics committee to the extent required. Apart from this, it is expressly understood that RUMC does not make any warranties regarding the DATA and specifically does not warrant or guarantee that the DATA will be accurate, be merchantable or useful for any particular purpose. RUMC cannot and shall not be held liable for any claims or damages by THIRD RECIPIENT or any third party, in connection with or as a result of the use of DATA by THIRD RECIPIENT. Unless and to the extent caused by RUMC's gross negligence or willful misconduct, THIRD RECIPIENT undertakes to hold harmless RUMC at all times against all of such damages or claims.

   In regards to the DATA and personal data breaches, THIRD RECIPIENT shall be responsible and liable for any damages, losses and fines resulting from its own failures to adhere to the terms of this Agreement and Applicable Data Protection Law and THIRD RECIPIENT shall indemnify and hold harmless RUMC for any of such damages.

The Parties' contact details for inquiries regarding handling and protection of DATA are as follows:

For RUMC, to:

RvB / Bestuurlijke en Juridische zaken / Privacy office
Postbus 9101 (route 632), 6500 HB Nijmegen
Geert Grooteplein Zuid 10 / Looproute 526
E-mail: privacy@radboudumc.nl
Phone number privacy office: 024-3616378 or internal 16378

For THIRD RECIPIENT, to:
Name: ….
Address: …..
e-mail:…..

10. THIRD RECIPIENT agrees in its use of the DATA to comply with all applicable international and national laws, statutes, regulations and guidelines.

11. THIRD RECIPIENT shall treat all CONFIDENTIAL INFORMATION as confidential for the duration of this Agreement including any extension thereof and thereafter for a period of five (5) years following termination or expiry of this Agreement. Excluded from this obligation of confidentiality shall be any CONFIDENTIAL INFORMATION of which the THIRD RECIPIENT can reasonably demonstrate that it (a) was previously known to THIRD RECIPIENT, or (b) is,

and/or becomes, publicly available during said five (5) year period through no fault of THIRD RECIPIENT, or (c) is independently and lawfully developed by the THIRD RECIPIENT. This obligation of confidentiality shall not apply to any disclosure required by law, provided that THIRD RECIPIENT shall notify RUMC of any disclosure required by law in sufficient time so that RUMC may contest such requirement, if RUMC so chooses. However, the foregoing exceptions shall not apply to: (a) CONFIDENTIAL INFORMATION contained within more general information that may fall within one or more of the exceptions, or (b) any combination of features or items of CONFIDENTIAL INFORMATION where one or more of the relevant individual features or items (but not the combination itself) may fall within one or more of the exceptions.

12. Parties acknowledge the importance of disseminating the results of the RECIPIENT'S RESEARCH PROJECT. Therefore, Third Recipient acknowledges that is has read and agrees to the publication rules as established in the POLARIS policy document. Before publication Third Recipient shall contact the original provider of the data to the POLARIS database and the POLARIS coordinator in order to establish further rules regarding co-authorship.

13. This Agreement will become effective on the Effective Date and will terminate two (2) years after the Effective Date. Parties can terminate this Agreement by giving a one (1) month prior written notice. Any clauses which will be expected or intended by its nature to survive the termination or the expiration of this Agreement, shall survive the termination or the expiration of this Agreement. Upon expiration or termination of this Agreement, the right to use the DATA and CONFIDENTIAL INFORMATION will automatically end and THIRD RECIPIENT will return or destroy all data received from RUMC. Upon request from RUMC, THIRD RECIPIENT shall confirm in writing the complete deletion of such DATA and CONFIDENTIAL INFORMATION.

14. In case of disputes where this Agreement does not provide a decisive answer, the Parties will consult each other before taking legal action. In case Parties cannot agree on such dispute and a Party initiates proceedings (as such an "Initiating Party") against the other Party (as such a "Defending Party") it shall do so at the competent court in Arnhem, the Netherlands. This Agreement will be construed, governed, interpreted and enforced in accordance with the laws of the Netherlands.

15. This Agreement will be binding upon and inure to the benefit of the respective successors and assignees of the parties hereto. However, THIRD RECIPIENT may not assign this Agreement in whole or in part without the prior written consent of the RUMC.

16. This Agreement represents this entire Agreement between the Parties with respect to the subject matter hereof, and may only be altered or amended by an instrument in writing signed by all of the Parties.

17. If any portion of this Agreement is in violation of any applicable regulation, or is unenforceable or void for any reason whatsoever, such portion will be inoperative and the remainder of this Agreement will be binding upon the parties. THIRD RECIPIENT represents that there are no agreements with any third party that might affect its ability to meet any of THIRD RECIPIENT's obligations under this Agreement.

18. Both Parties acknowledge that the signatories to this Agreement are authorized representatives of each of the Parties and legally authorized to sign this Agreement.

19. If the lawful performance of any part of this Agreement by a Party is rendered impossible by

or as a result of any cause beyond such Party's reasonable control, such Party will not be considered in breach hereof as a result of failing so to perform.

IN WITNESS WHEREOF, the parties have executed this Agreement, in duplicate originals, as of the Effective Date.

For **RUMC**

By:_____
Name: J. Sjoerts
Title: Director Tech Transfer Office
Date:_____

By:_____
Name: prof. R. Bindels
Title: Head of the Dept. of Physiology
Date:_____

READ AND ACKNOWLEDGED:

_____
Dr. L. M. Buffart

For **THIRD RECIPIENT**,

By:_____
Name:
Title:
Date:_____

By:_____
Name:
Title:
Date:_____

READ AND ACKNOWLEDGED:

_____
THIRD RECIPIENT'S SCIENTIST

ANNEX I

Description of the DATA

ANNEX II

Research Plan

Appendix D

Third recipient agreement POLARIS

Appendix E: POLARIS Data Sharing Agreement – THIRD RECIPIENT

ACQUIRING
PSEUDONYMIZED PERSONAL DATA – POLARIS
(Predicting Optimal cAncer Rehabilitation and Supportive care)

A20-xxxx

This agreement (hereinafter referred to as "Agreement") is made and entered by and between:

Stichting Radboud Universitair Medisch Centrum established at Geert Grooteplein 10, P.O. Box 9101, 6500 HB Nijmegen, the Netherlands, represented by its legal representative, J. Sjoerts, hereinafter referred to as "RUMC";

and

<…>, established at , **other** >, represented by its legal representative <…>, hereinafter referred to as "Third Recipient".

Hereinafter jointly referred to as "Parties" and individually as "Party";

WHEREAS

a) RUMC has obtained data from Providers in the POLARIS database("DATA")
b) THIRD RECIPIENT, through **<…>**, hereinafter referred to as "THIRD RECIPIENT SCIENTIST", has requested RUMC, through **<…>**, hereinafter referred to as "RUMC'S SCIENTIST", to provide THIRD RECIPIENT with the DATA for use by THIRD RECIPIENT'S SCIENTIST for the purpose of its RESEARCH PLAN
c) The purpose and means of the RESEARCH PLAN have been determined by THIRD RECIPIENT;
d) RUMC is willing, subject to the terms and conditions of this Agreement and the POLARIS policy document, to provide the DATA to THIRD RECIPIENT.
e) The POLARIS policy document is an integral part of this Agreement and has been provided to Third Recipient.

I Definitions

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3. EFFECTIVE DATE: The date of last signing of this Agreement.
4. INVENTION: any invention, discovery , improvement, material, signal, process, formula, know-how or other innovation related to or arising from the use of the DATA and/or CONFIDENTIAL INFORMATION , whether patentable or not and obtained as a result of the performance of the RESEARCH PLAN.
5. CONFIDENTIAL INFORMATION: All information, know-how, data and experience of RUMC regarding the DATA, its characteristics, RUMC's research concerning the DATA, whether of a scientific, technical, engineering, operational, or economic nature, supplied to or obtained by THIRD RECIPIENT in written form, in the form of drawings or in the recording of oral conversation, or samples, which is reasonably required by THIRD RECIPIENT for performance

of RESEARCH PLAN.

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b) With respect to the DATA, THIRD RECIPIENT shall be considered to be a separate data controller under the GDPR for the processing of the DATA for its RESEARCH PLAN.
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d) If THIRD RECIPIENT becomes aware of a personal data breach, THIRD RECIPIENT shall promptly notify RUMC. In such a case Parties will fully cooperate with each other to remedy the personal data breach, fulfill the (statutory) notification obligations timely and cure any damages. A personal data breach refers to: 1) a personal data breach as meant in article 34a of the Dutch Data Protection Act, and 2) as of 25 May 2018, a personal data breach as meant in articles 33 and 34 of the European General Data Protection Regulation.
e) In the event that a person from whom DATA was obtained, withdraws his/her informed consent for the use thereof, RUMC shall supply THIRD RECIPIENT with sufficient information and THIRD RECIPIENT shall immediately cease all use of the relevant DATA and shall delete all copies of the relevant DATA. Upon request from RUMC, THIRD RECIPIENT shall confirm in writing the complete deletion of such DATA.
f) RUMC shall be data controller of the DATA under the GDPR up until the moment the DATA is provided to THIRD RECIPIENT.

3. The THIRD RECIPIENT and the THIRD RECIPIENT SCIENTIST agree that the DATA: (a) is to be used only for the academic purposes as described in the RESEARCH PLAN; (b) will not be used for commercial purposes and (c) will not be transferred to a third party. THIRD RECIPIENT shall not carry out the RESEARCH PLAN with any third party or entity without prior written approval of RUMC. THIRD RECIPIENT shall not attempt in any way to obtain the identity of the people to which the DATA relates.

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   In regards to the DATA and personal data breaches, THIRD RECIPIENT shall be responsible and liable for any damages, losses and fines resulting from its own failures to adhere to the terms of this Agreement and Applicable Data Protection Law and THIRD RECIPIENT shall indemnify and hold harmless RUMC for any of such damages.

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Geert Grooteplein Zuid 10 / Looproute 526
E-mail: privacy@radboudumc.nl
Phone number privacy office: 024-3616378 or internal 16378

For THIRD RECIPIENT, to:
Name: ….
Address: …..
e-mail:…..

10. THIRD RECIPIENT agrees in its use of the DATA to comply with all applicable international and national laws, statutes, regulations and guidelines.

11. THIRD RECIPIENT shall treat all CONFIDENTIAL INFORMATION as confidential for the duration of this Agreement including any extension thereof and thereafter for a period of five (5) years following termination or expiry of this Agreement. Excluded from this obligation of confidentiality shall be any CONFIDENTIAL INFORMATION of which the THIRD RECIPIENT can reasonably demonstrate that it (a) was previously known to THIRD RECIPIENT, or (b) is,

and/or becomes, publicly available during said five (5) year period through no fault of THIRD RECIPIENT, or (c) is independently and lawfully developed by the THIRD RECIPIENT. This obligation of confidentiality shall not apply to any disclosure required by law, provided that THIRD RECIPIENT shall notify RUMC of any disclosure required by law in sufficient time so that RUMC may contest such requirement, if RUMC so chooses. However, the foregoing exceptions shall not apply to: (a) CONFIDENTIAL INFORMATION contained within more general information that may fall within one or more of the exceptions, or (b) any combination of features or items of CONFIDENTIAL INFORMATION where one or more of the relevant individual features or items (but not the combination itself) may fall within one or more of the exceptions.

12. Parties acknowledge the importance of disseminating the results of the RECIPIENT'S RESEARCH PROJECT. Therefore, Third Recipient acknowledges that is has read and agrees to the publication rules as established in the POLARIS policy document. Before publication Third Recipient shall contact the original provider of the data to the POLARIS database and the POLARIS coordinator in order to establish further rules regarding co-authorship.

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14. In case of disputes where this Agreement does not provide a decisive answer, the Parties will consult each other before taking legal action. In case Parties cannot agree on such dispute and a Party initiates proceedings (as such an "Initiating Party") against the other Party (as such a "Defending Party") it shall do so at the competent court in Arnhem, the Netherlands. This Agreement will be construed, governed, interpreted and enforced in accordance with the laws of the Netherlands.

15. This Agreement will be binding upon and inure to the benefit of the respective successors and assignees of the parties hereto. However, THIRD RECIPIENT may not assign this Agreement in whole or in part without the prior written consent of the RUMC.

16. This Agreement represents this entire Agreement between the Parties with respect to the subject matter hereof, and may only be altered or amended by an instrument in writing signed by all of the Parties.

17. If any portion of this Agreement is in violation of any applicable regulation, or is unenforceable or void for any reason whatsoever, such portion will be inoperative and the remainder of this Agreement will be binding upon the parties. THIRD RECIPIENT represents that there are no agreements with any third party that might affect its ability to meet any of THIRD RECIPIENT's obligations under this Agreement.

18. Both Parties acknowledge that the signatories to this Agreement are authorized representatives of each of the Parties and legally authorized to sign this Agreement.

19. If the lawful performance of any part of this Agreement by a Party is rendered impossible by

or as a result of any cause beyond such Party's reasonable control, such Party will not be considered in breach hereof as a result of failing so to perform.

IN WITNESS WHEREOF, the parties have executed this Agreement, in duplicate originals, as of the Effective Date.

For **RUMC**

By:_____
Name: J. Sjoerts
Title: Director Tech Transfer Office
Date:_____

By:_____
Name: prof. R. Bindels
Title: Head of the Dept. of Physiology
Date:_____

READ AND ACKNOWLEDGED:

_____
Dr. L. M. Buffart

For **THIRD RECIPIENT**,

By:_____
Name:
Title:
Date:_____

By:_____
Name:
Title:
Date:_____

READ AND ACKNOWLEDGED:

_____
THIRD RECIPIENT'S SCIENTIST

ANNEX I

Description of the DATA

ANNEX II

Research Plan

Appendix E

Employment agreement the Netherlands comprehensive cancer organisation (IKNL)

Date 10 March 2023
Reference HR/IB
Re Hospitality Agreement

Postbus 19079 3501 DB Utrecht

Ms. B.W. Western
Nieuwe Emmasingel 1
5611 AM Eindhoven

locatie Utrecht
Godebaldkwartier 419
3511 DT Utrecht
Postbus 19079
3501 DB Utrecht

t 088 234 60 00
f 088 234 60 01
www.iknl.nl

Dear Ms. Western, dear Benedikte,

It gives me pleasure to submit herewith two copies of the hospitality agreement between you and the Netherlands Comprehensive Cancer Organisation (IKNL). Aside from the agreement, please also find a non-disclosure agreement.

We look forward to receiving a signed copy (and initialed if applicable) of both agreements within 7 days in enclosed return envelope (free return).

Do you have any questions, or would you like a further explanation? Please contact the HR department (hr@iknl.nl).

We look forward to a pleasant collaboration!

Yours sincerely,

I.P.M.(Irma) van Beuningen
Head HR

Attachment(s) Hospitality Agreement (2x)
Non-disclosure Agreement (2x)
Return envelope

Hospitality Agreement

The undersigned:

Netherlands Comprehensive Cancer Organisation foundation,
with its registered offices in Utrecht, hereinafter referred to as 'IKNL', legally represented herein by I.P.M. (Irma) van Beuningen, head HR,

and

B.W. Western, residing at Nieuwe Emmasingel 1 , 5611 AM Eindhoven,
born on 31 January 1994,
Hereinafter referred to as: employee,

Taking into consideration that Employee is appointed as external researcher as part of her employment for Employer, in which Employer acts as employer of the Employee, and it is expressly not the intention to create any employment with IKNL.

hereby declare to have entered into a Hospitality Agreement under the following conditions:

Article 1 - Nature of the Hospitality Agreement
For implementation of the activities, Employee is given access at IKNL to: profile external researcher. This access applies for activities related to. Physical activity after gynaecological cancer.

Article 2 - Duration of the Hospitality Agreement
The Hospitality Agreement is entered into for a period of one year, from 1st April 2023 to 30th April 2023 with the option to extend this. Not later than one month before termination of the agreement, the Employer and IKNL will decide in mutual consultation with Employee about renewal or non-renewal thereof.

Article 3 - Premature termination
The Hospitality Agreement may be prematurely terminated by both parties. The premature notice period for both Employer, IKNL and the Employee is one month.

Article 4 - Confidentiality
Employee must maintain strict confidentiality of personal and medical data obtained during implementation of the activities. Without prejudice to official regulations, no information will be provided to any person or authority which is traceable to the registered person, an institution or party responsible for providing information.

Article 5 - Liability
The Employer of the Employee is obliged to compensate any damages and consequential loss suffered by IKNL and third parties.

Article 6 - Issuances
Employee declares to have received from IKNL a token on loan for use: A hard token must be returned to IKNL upon termination of the agreement. If it relates to a soft token, this must be de-installed upon termination.

Article 7 - Guiding
IKNL will provide Employee with instructions for the planning and implementation of activities.

Thus, drawn up, agreed to and signed in duplicate, in Utrecht on 10 March 2023.

IKNL:

I.P.M. (Irma) van Beuningen
Head HR

Employee:

Benedikte Western

B.W. Western

Non-Disclosure Agreement

The undersigned, namely:

the Stichting **Integraal Kankercentrum Nederland** (IKNL, Foundation of the Netherlands Comprehensive Cancer Organisation), having its registered offices in (3511 DT) Utrecht at Godebaldkwartier 419, legally represented in this matter I.P.M. (Irma) van Beuningen, head HR of the Foundation of the Netherlands Comprehensive Cancer Organisation, hereinafter referred to as 'IKNL';

and

B.W. Western, residing at Nieuwe Emmasingel 1 ,5611 AM Eindhoven, hereinafter referred to as the 'Contractor';

Take into consideration that:

- The Contractor has entered into a contract with the Foundation of the Netherlands Comprehensive Cancer Organisation (IKNL);
- IKNL is active in the field of oncology and palliative care and seeks to serve the public interest by promoting the fight against cancer, particularly by caring for people suffering from cancer and improving palliative care, and furthermore, everything that is otherwise related directly or indirectly or that could be beneficial for that purpose;
- In view of the above, IKNL implements (registry)activities in the broadest sense of the word;
- In the performance of their activities for IKNL, the Contractor is directly or indirectly involved in these (registry)activities;
- In the performance of these (registry)activities, (personal) data or files or documents or documents derived from it can possibly become known to the Contractor that are classified as confidential or secret or it is reasonably understood that the contents is to be treated as confidential and which information does not belong in the public domain;
- In legal terms, IKNL is obliged to maintain confidentiality regarding personal data and data sets and all documents derived from them from which it obtains knowledge;
- Also, in contracts between IKNL and its collaborating partners with respect to the (registry)activities, full confidentiality has been agreed to regarding files and personal data and documents derived from them:
- In extension of this legal provision and also in extension of these contracts with collaborating partners, for the benefit of the (registry)activities IKNL is also obliged to agree to such a confidentiality obligation with the Contractors who are employed on a temporary basis;
- This agreement serves for that purpose;
- This agreement is attached to and is comprehensively part of the aforesaid agreement of assignment;

Agree as follows:

1. The Contractor endeavours to maintain strict confidentiality towards third parties with regard to all information gained by them as a result of their assignment and the (registry)activities entrusted to them in any manner whatsoever and of which its confidential character is indicated or is to be reasonably suspected by them. The

Contractor may only provide the aforesaid confidential information to third parties with the express prior written consent from IKNL;

2. The Contractor may not use for their own benefit nor for the benefit of third parties any information that becomes known in the performance of their activities and which he/she knows, or has reasonable grounds to believe that it is of a confidential nature;
3. The Contractor declares that they will not disclose the existence, nature and content of collaborations with third parties with regard to the (registry)activities;
4. The Contractor is aware that on commencement of a new (interim) assignment or upon termination of their current (interim) assignment in the context of this non-disclosure agreement accepted obligations remain in force and in case of violation of these obligations they remain subject to the sanctions laid down by law and in this declaration;
5. In the event of violation by the Contractor of the obligations vested in them by law or pursuant to this agreement, the Contractor forfeits to and for the benefit of IKNL an immediately due and payable fine, without summons or notice of default, of € 2,500.00 for each infringement and for each day or part thereof that the violation continues, without prejudice to the right of IKNL to claim full compensation instead of the fine;
6. The Contractor declares that their attention has expressly been drawn to their obligations and responsibilities in respect of the performance of their activities.

Thus agreed to and drawn up in duplicate, initialled on each page and signed in Utrecht, on 10 March 2023.

I.P.M. (Irma) van Beuningen
Head HR

B.W. Western

Appendix F

The Health Education Impact Questionnaire (HeiQ)

ID No. _____

heiQ
health education impact questionnaire

Version 3.0

Instructions

Thank you for taking the time to participate in this survey.

There are no right or wrong answers but please make sure that you answer every question the best you can.

heiQ template updated June 2015

Instructions

Please indicate how strongly you disagree or agree with the following statements by checking the response that best describes you now.

Example

Ms Jane Citizen has answered these questions in the following way:

Check a box by crossing it.

☐ ☐ ☐ ☒

Questions:

		Right now			
		Strongly disagree	Disagree	Agree	Strongly agree
1	I am doing some of my hobbies	☐	☐	☒	☐
2	I have a plan to do physical activity	☐	☒	☐	☐

For Question 1, Jane's answer shows that right now she agrees that she has been doing some of her hobbies lately.

For Question 2, Jane disagrees with the statement that right now she has a plan to do physical activity.

Please answer the following questions.

Check a box by crossing it:

☐ ☐ ☐ ☒

		Right now			
		Strongly disagree	Disagree	Agree	Strongly agree
1	On most days of the week, I do at least one activity to improve my health (e.g., walking, relaxation, exercise)	☐	☐	☐	☐
2	Most days I am doing some of the things I really enjoy	☐	☐	☐	☐
3	As well as seeing my doctor, I regularly monitor changes in my health	☐	☐	☐	☐
4	I often worry about my health	☐	☐	☐	☐
5	I try to make the most of my life	☐	☐	☐	☐
6	I know what things can trigger my health problems and make them worse	☐	☐	☐	☐
7	My health problems make me very dissatisfied with my life	☐	☐	☐	☐
8	I am doing interesting things in my life	☐	☐	☐	☐

Right <u>now</u>

Check a box by crossing it:

☐ ☐ ☐ ☒

		Strongly disagree	Disagree	Agree	Strongly agree
9	I do at least one type of physical activity every day for at least 30 minutes (e.g., walking, gardening, housework, golf, bowls, dancing, Tai Chi, swimming)	☐	☐	☐	☐
10	I have plans to do enjoyable things for myself during the next few days	☐	☐	☐	☐
11	I have a very good understanding of when and why I am supposed to take my medication	☐	☐	☐	☐
12	I often feel angry when I think about my health	☐	☐	☐	☐
13	On most days of the week, I set aside time for healthy activities (e.g., walking, relaxation, exercise)	☐	☐	☐	☐
14	I feel hopeless because of my health problems	☐	☐	☐	☐
15	I feel like I am actively involved in life	☐	☐	☐	☐
16	When I have health problems, I have a clear understanding of what I need to do to control them	☐	☐	☐	☐
17	I carefully watch my health and do what is necessary to keep as healthy as possible	☐	☐	☐	☐
18	I get upset when I think about my health	☐	☐	☐	☐
19	I walk for exercise, for at least 15 minutes per day, most days of the week	☐	☐	☐	☐
20	With my health in mind, I have realistic expectations of what I can and cannot do	☐	☐	☐	☐
21	If I think about my health, I get depressed	☐	☐	☐	☐
22	If I need help, I have plenty of people I can rely on	☐	☐	☐	☐
23	I have effective ways to prevent my symptoms (e.g., discomfort, pain and stress) from limiting what I can do in my life	☐	☐	☐	☐
24	I have very positive relationships with my healthcare professionals	☐	☐	☐	☐
25	I have a very good idea of how to manage my health problems	☐	☐	☐	☐
26	When I have symptoms, I have skills that help me cope	☐	☐	☐	☐
27	I try not to let my health problems stop me from enjoying life	☐	☐	☐	☐

Right <u>now</u>

Check a box by crossing it:

☐ ☐ ☐ ☒

		Strongly disagree	Disagree	Agree	Strongly agree
28	I have enough friends who help me cope with my health problems	☐	☐	☐	☐
29	I communicate very confidently with my doctor about my healthcare needs	☐	☐	☐	☐
30	I have a good understanding of equipment that could make my life easier	☐	☐	☐	☐
31	When I feel ill, my family and carers really understand what I am going through	☐	☐	☐	☐
32	I confidently give healthcare professionals the information they need to help me	☐	☐	☐	☐
33	I get my needs met from available healthcare resources (e.g., doctors, hospitals and community services)	☐	☐	☐	☐
34	My health problems do not ruin my life	☐	☐	☐	☐
35	Overall, I feel well looked after by friends or family	☐	☐	☐	☐
36	I feel I have a very good life even when I have health problems	☐	☐	☐	☐
37	I get enough chances to talk about my health problems with people who understand me	☐	☐	☐	☐
38	I work in a team with my doctors and other healthcare professionals	☐	☐	☐	☐
39	I do not let my health problems control my life	☐	☐	☐	☐
40	If others can cope with problems like mine, I can too	☐	☐	☐	☐