September 2019 (CSTG-19) Competition Awarded CCS/CIHR Cancer Survivorship Team Grants, in partnership with the Alberta Cancer Foundation

Listed in alphabetical order

Cafazzo, Joseph
The Toronto Hospital (General Division) - UHN

Virtualizing survivorship: implementing a more timely and comprehensive model of follow-up care

Problem

Trends in prostate cancer (PCa) and breast cancer (BCa) survivorship demand effective and sustainable models of post-treatment follow-up care. The most acute of these trends is disease prevalence; PCa and BCa are the most common cancers in Canadian men and women—1 in 7 and 1 in 8—respectively. Early diagnosis and effective treatment have increased survival rates with the number of cancer survivors increasing correspondingly. However, cancer survivors are often left with myriad undesired functional impairments after treatment, as well as psychosocial and mental health challenges that diminish their quality of life. The current model of care has limited capacity and time to provide comprehensive follow-up that meets endorsed survivorship practice guidelines.

In recent years, the pursuit of “virtual care” in cancer follow-up has garnered interest but has not been implemented or studied widely. Broadly defined as any remote interaction between patients and healthcare providers using technology to enhance the quality and effectiveness of care, virtual cancer care models exploit technological innovation to deliver integrated, stratified, and tailored survivorship care to patients who are at low risk of recurrence. Building on the viability of these virtual models, our research group was awarded a CCS/CIHR Innovation Grant in August 2018 to design, develop, and implement three virtual PCa clinics – the *Ned* Virtual Clinics – across Ontario to address survivor needs at scale, reduce the burden of care, improve the survivorship experience, and increase quality of life.

Objectives

We seek to advance our foundational work on the *Ned* Virtual Clinics and their impact on Canadian survivorship outcomes through pursuing five new virtual care initiatives: (1) spread our current virtual PCa clinic model to two new sites in Halifax and Calgary; (2) develop and validate a computational survivorship algorithm to stratify patients based on need, risk, and eligibility for transition to primary care for follow-up; (3) introduce a new *Ned* Nurse to review survivorship outcomes, triage patients to appropriate care providers and services, and provide care in between/in place of scheduled virtual visits; (4) adapt this virtual PCa survivorship model to inform the concept and service design of a virtual BCa clinic, and (5) explore new models of funding in Ontario, Nova Scotia, and Alberta for virtual survivorship services to mitigate the policy and economic barriers of sustaining virtual models of care.

Methods

We will conduct a hybrid type 2 implementation-effectiveness multi-method study of introducing nurse-led virtual survivorship care into oncological practice, with an embedded historical control study comparing the outcomes of 300 men enrolled in the *Ned* Virtual Clinics with 300 men receiving traditional follow-up care.

Significance

This work will attempt to address the notable gaps in the care for survivors that are living longer with the effects of their disease, its treatment, and their resultant complex psychosocial and medical needs. It will constitute a modernization of the model of survivorship care that recognizes what has changed in patient expectations and how the health system requires a more appropriate use of human and technological resources to address these expectations. At project end, our intention is to have five nurse-led, algorithm-enhanced *Ned* Virtual Clinics implemented across Canada that are localized and integrated with traditional models of survivorship care, each serving as a sustainable model of follow-up management and care that optimizes healthcare system capacity and better addresses individualized survivorship needs at scale.

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Dissemination, implementation, and effectiveness of the exercise oncology survivorship partnership model: reaching rural cancer survivors to enhance quality of life

Summary: As cancer survivorship numbers grow, a focus on positive health in survivorship is essential. Exercise is an evidence-based effective self-management strategy that benefits all cancer survivors (CS). However, the majority of research, and the limited development of evidence-based clinical or community programs in exercise and cancer, has been conducted almost exclusively in urban academic and clinical settings. Very limited implementation outreach to "hard to reach" CS, such as those in rural or non-urban environments, has occurred. There are unique features of the rural environment that are significant barriers to cancer care in general, and to supportive cancer care resources in particular, such as geographic diversity, limited access/travel distances to resources and facilities, and lack of trained personnel to implement survivorship services. Rural CS (RCS), or those living in non-urban settings (defined as <100,000 in population), report higher cancer burden from diagnosis through treatment and into survivorship. This burden is associated with inequitable access to supportive cancer care resources, including exercise programs, resulting in RCS experiencing more negative effects after treatment than their urban counterparts and being overall less healthy.

In this proposed cancer exercise hybrid implementation effectiveness research, we will use an integrated knowledge translation approach to move the current evidence-base that clearly supports the role of exercise for CS, into sustainable and effective community-based rural settings that will optimize the delivery of exercise to RCS. Our team has spearheaded national collaborations to connect CS to exercise programs. These implementation and dissemination projects, with demonstrated success, are facilitated by partnerships between the cancer care system (clinics/hospitals) and community-based fitness facilities. Such programs are essential to ensure effective exercise programming is ***sustainable*** and ***widely available*** to the growing population of RCS.

Objectives: To disseminate, implement, and assess the effectiveness of our Exercise Oncology Survivorship (EOS) partnership model to increase the reach and delivery of exercise programs to RCS. Reaching *more RCS with an exercise program enhances equitable access to supportive cancer care resources that will enhance cancer survivorship, providing fitness, health, and psychosocial benefits.*

Methods. Using implementation science and a focus on the *reach* of our EOS partnership model to RCS, we will use the: (1) CIHR knowledge to action framework to guide the process of translating research evidence into practice; (2) Capability, Opportunity, Motivation and Behaviour to understand and explain influences on implementation outcomes; and, (3) RE-AIM framework to evaluate implementation and support of programming at sites, which includes assessment of the reach, effectiveness, adoption, implementation and maintenance of establishing rural community exercise oncology programs. Specifically, we will assess the dissemination and implementation of the EOS model, using markers of reach (numbers), implementation (training, logistics, delivery) and maintenance (ongoing delivery, sustainability measures). Effectiveness of the exercise program for participants will be captured through objective exercise behaviour data, participant-reported physical and psychosocial outcomes, and program satisfaction. Approximately 45-50 sites and over 1500 RCS participants will be targeted over 5 years, starting in AB and NS, and moving implementation to Atlantic regions, BC, SK, and ON.

Significance: Given our previous implementation success, we will extend the reach of our EOS partnership model across Canada and change the exercise levels of RCS. Our impacts include increased access to supportive cancer care resources that will enhance the QOL of more Canadian CS. Specifically targeting the clinically underserved population of RCS creates equity in access to these resources that build health and wellness in cancer survivorship.

Jones, Jennifer
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Canadian cancer rehabilitation (CanRehab) team: improving the systematic identification, management, and treatment of the adverse effects of cancer

Background: Given the growing population of cancer survivors and the high documented rates of adverse treatment effects, functional loss and disability, cancer rehabilitation is becoming increasing relevant. There is urgent need for research that can inform survivorship care including the proactive identification and assessment of disabling sequelae and the development and assessment of sustainable personalized cancer rehabilitation interventions. **Objectives:** The current proposal brings together a large group of patients, researchers, and clinicians across Canada and includes three concurrent projects focused on improving access to effective, appropriate, and timely *cancer rehabilitation (CanRehab Team)*. *Project One* will develop, implement and evaluate an innovative electronic prospective surveillance and decision support system for cancer rehabilitation. This will involve standardized remote monitoring of cancer rehabilitation needs at pre-defined time points during cancer care and a risk stratified automated response system to deliver support and care including links to education and lifestyle counselling, community based and on-line support, and/or alerts for further clinical screening. *Project Two* will test the effectiveness of a virtual cancer rehabilitation program for patients with cancer related impairments and explore factors that affect implementation. *Project Three* will develop and test the feasibility of an in-person group based cancer rehabilitation program for patients with stable metastatic disease focused on maximizing potential for independent function and quality of life. **Methods:** The ***CanRehab*** projects will be conducted at BC Cancer, Princess Margaret Cancer Centre, Saint John Regional Hospital, and Dr. H Bliss Murphy Cancer Centre and will include breast, colorectal, head and neck and lymphoma cancer sites. **Project One:** i) Development and implementation of the prospective surveillance and decision support system for cancer rehabilitation *(CanRehab360)* (Phase 1): Development and design of CanRehab360 will involve a four step engagement process (Immerse and Understand; Concept Design; Design and Test; Development and Launch) that will enable both up-front and ongoing engagement with patients and other key stakeholders, to ensure the design and development of a solution that is meaningful and impactful. ii) Deployment and evaluation of *CanRehab360* (Phase 2): Using a pragmatic trial design and multiple outcomes model, will evaluate the effectiveness of *CanRehab360* on health system/process outcomes (access to appropriate care, health care utilization, sensitivity/specificity of alerts) and patient level outcomes (symptom burden, disability, function, quality of life, satisfaction with care, engagement in health behaviours). Phase 2 will also include a process evaluation to understand the mediating factors leading to outcomes. **Project Two:** We will conduct a hybrid type I randomized comparative effectiveness/implementation trial of an 8-week structured virtual cancer rehabilitation intervention (CaRE@Home) that includes the use of wearable technology, an exercise app to support tailored exercise prescriptions, interactive on-line education modules and health coaching. Outcomes include disability and function (primary outcomes) as well as quality of life, distress, work status, physiological outcomes and health behaviours. Using the Consolidated Framework for Implementation Research, we will also identify potential factors that may affect successful implementation and integration of CaRE@Home in different cancer settings. **Project Three:** We will conduct a Phase 2 exploratory RCT to assess feasibility and acceptability of a structured group cancer rehabilitation intervention for people with stable metastatic cancer and determine an estimate of intervention efficacy on functional outcomes. **Significance:** There remains an urgent call to action to invest in the recovery and well-being of cancer survivors. Through these projects, we seek to improve the systematic identification and management of cancer-related adverse effects in order to regain/maximize function, independence and improve quality of life.

Leong, Darryl
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Addressing cardiovascular co-morbidities in patients with cancer (C3)

Summary
Increased survival with cancer and cardiotoxicity of some cancer treatments are leading to an increased number of patients developing cardiovascular disease. Moreover, many cancers and cardiovascular diseases share common determinants. Therefore, cardiovascular disease is a major cause of morbidity and mortality in cancer survivors. We propose two research projects that will address two key cardiovascular problems 1) in men with prostate cancer and 2) in individuals with breast cancer who develop cardiotoxicity from trastuzumab, which is an important life-prolonging therapy for many breast cancer survivors.

Objectives

1.To evaluate whether a cardiovascular physician should be part of the care team for prostate cancer survivors

2.To evaluate the benefits and risks of continuing trastuzumab in breast cancer survivors who develop mild cardiotoxicity from trastusuzumab

Methodology

1.This proposal will enable the completion of a randomized, controlled trial evaluating the effects of a cardiovascular intervention in men with newly diagnosed prostate cancer or those prescribed androgen deprivation therapy for the first time. The intervention group are referred to a cardiovascular physician who will address cardiovascular risk factors in a standardized manner, while the control group will receive usual standard-of-care. To date, we have randomized 1400 participants in the vanguard phase of this trial; we aim to randomize a further 1400 participants. Focus group interviews will be performed to help us understand the barriers to and facilitators of adoption of good cardiovascular care in these participants.

2.In patients with breast cancer who develop cardiotoxicity from trastuzumab, we will undertake a randomized, controlled trial evaluating the safety and efficacy of a strategy of ongoing trastuzumab therapy accompanied by the prescription of angiotensin converting enzyme inhibitors and beta-blockers, versus guideline-driven discontinuation of trastuzumab. We will also perform long-term follow-up of women who have developed trastuzumab cardiotoxicity to understand the late sequelae of this complication.

Significance

Cardiovascular disease accounts for nearly as many deaths among men with prostate cancer as the cancer itself. To date, this has been a largely neglected aspect of their care. The randomized trial proposed is a unique trial that will inform a new model of care for prostate cancer survivors.

For breast cancer survivors receiving trastuzumab, completion of trastuzumab therapy reduces the risk of death. To have this hope taken away because of mild and potentially reversible heart injury can be devastating. While guidelines suggest that trastuzumab should be withheld or discontinued in these individuals, the guidelines are not based on high quality evidence. In this proposal, we challenge this evidence and aim to develop an approach that can optimize the delivery of a life-prolonging therapy for breast cancer.

Mabbott, Donald
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Phase III randomized double-blind placebo-controlled trial of metformin for cognitive recovery and white matter growth in paediatric medulloblastoma patients

A critical barrier to improving the quality of life of children/adolescents living with cancer is that the disease and curative therapies can have toxic effects on healthy tissue, which result in long term problems. This is no truer than for children and adolescents who survive medulloblastoma: they experience brain injury and cognitive impairment. There are few therapies for restoring cognitive function and promoting brain growth in survivors; however exciting new work in regenerative medicine offers hope. The drug metformin promotes brain growth in animal models by activating neural stem cells. In a pilot trial, we found that metformin was safe and tolerable for use in children/adolescents treated for a brain tumour with cranial radiation and may have potential to improve cognition and promote white matter growth. Here we propose to test the efficacy of treatment with metformin for cognitive recovery and brain growth. Specifically, we ask: In children/adolescents aged 5 to 17 years who have completed treatment for medulloblastoma, is oral administration of metformin for 16 weeks associated with greater improvement of cognitive function and brain growth compared to placebo administered for 16 weeks?
We propose a national multi-site phase III double blind randomized controlled parallel arm trial with a primary outcome of behavioral measures of information processing speed, working memory, and auditory-verbal declarative memory. The key secondary outcome will be diffusion MRI within the corpus callosum. Exploratory measures will include diffusion MRI of global white matter and structural MRI of hippocampal volume. We also seek to examine long-term effectiveness at 24 weeks following completion of metformin treatment as an exploratory outcome. Participants will be randomly assigned to complete either a 16-week cycle of Metformin or a 16-week cycle of placebo. Outcome assessment will be conducted at baseline, at 16 weeks from baseline immediately following treatment, and at 6 months following completion of treatment. Metformin is a well-studied medication with a broad clinical experience in children including polycystic ovarian syndrome, diabetes, and obesity. The youngest age of use is 2 years old. The proposed dose and the schedule of administration of metformin is based on safety and toxicity data obtained from our pilot trial and previous use in paediatric populations. 70 participants – aged 5-17 years - will be recruited at 8 sites that are part of the Canadian Paediatric Brain Tumour Consortium, including British Columbia Children's Hospital, Stollerly Children's Hospital, Alberta Children's Hospital, Saskatoon Health Region, The Hospital for Sick Children, Children's Hospital of Eastern Ontario, Centre Mère-Enfant Soleil du CHU de Québec, and the IWK Health Centre. The proposed sample size is based on the number of eligible patients at each site as well as recruitment and participation and retention rates estimated from the pilot trial that was conducted at the Hospital for Sick Children. ANCOVA will be used to examine the effects metformin versus placebo for each outcome, controlling for baseline outcome measurement. By commencing this clinical trial, we can accelerate progress for improving physical and behavioral function in survivors of medulloblastoma. Our work has the potential to exert both a sustained and powerful influence upon future clinical trials and improve patient quality of life. If we find positive effects on brain health by using metformin, then this could lead to a dramatic shift in the approach to treating cognitive disability in children/teenagers with cancer, one where we treat late effects in the same manner as the primary disease – through rigorous, multi-site, and multi-modality clinical trials. By focusing on a disease that requires some of the most aggressive therapy used in modern protocols, and by targeting the patients most vulnerable to the harmful effects of treatment we hope to provide a model of intervention that can then be applied to other cancers and actively promote brain health and cognitive recovery.

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The Harmonized Interventions to Maintain health via Appropriate risk factor modification and Lifestyle changes in pediatric, Adolescent and Young Adult cancer Survivors (HIMALAYAS) trial

Background: Improved cancer treatments have led to an exponential growth in the number of pediatric, adolescent and young adult cancer survivors (PAYA-CS). PAYA-CS have >2-fold higher risk for cardiovascular disease (CVD) relative to age-matched controls and an 11-fold increased risk of CVD mortality. This is driven by treatment-related injury and secondary onset of CVD risk factors, including low cardiopulmonary fitness (VO_{2peak}), diabetes, and hypertension. CVD risk in PAYA-CS may be exacerbated by mental health issues (e.g., anxiety). However, no interventions have been established to mitigate these threats to PAYA-CS' health. Exercise therapy is a cornerstone of CVD prevention and treatment. The American Cancer Society recently endorsed exercise-based cardiac rehabilitation (CR) to prevent CVD in cancer survivors. However, PAYA-CS have unique needs that are not addressed in existing traditional CR programs. In this grant, we propose to test the efficacy of a cardio-oncology rehabilitation (**CORE**) model geared to the needs of PAYA-CS. This will be compared against exercise behavioural support only **(SUPPORT)**. We will focus our intervention on higher risk PAYA-CS with mild heart dysfunction (referred to as stage B heart failure – S_BHF). We will also create a parallel observational cohort (**OBS**) for comparison. We will also collaborate with the Canadian Partnership for Tomorrow Project (CPTP) for life-long follow-up of the health status of these participants.

Objectives: To determine differences in (1) $VO2_{peak}$ between CORE and SUPPORT between baseline (T0) and 6 months (T1). (2) cardiac function and CVD risk factor control (blood pressure, dyslipidemia, dysglycemia), and patient reported outcomes (PROs) between T0 and T1, (3) trajectories in all above outcomes between T0, T1, 12 months (T2) and 24 months (T3) between CORE and SUPPORT, and between T0 and T3 between CORE, SUPPORT, and OBS groups (4) to establish a large cohort of PAYA-CS for life long follow-up for CVD events.

Methods: We propose two-arm randomized controlled trial (RCT) with a parallel observational arm. PAYA-CS will be enrolled from CPTP, 5 cancer centres (in Toronto, Montreal, Halifax, Edmonton, Vancouver), and self-referrals. Inclusion criteria are: 1) developed cancer before age 39; 2) current age between 18 and 49 years; 3) received treatments associated with high CVD risk. An additional criterion for inclusion in the RCT is S_BHF, defined as left ventricular ejection fraction 40-53% (LVEF), global longitudinal strain (GLS) >-18.0%, or presence of diastolic dysfunction (DD). Participants with S_BHF who consent for the RCT will be randomized to CORE or SUPPORT (total sample size 336). Screened PAYA-CS without S_BHF and those not enrolled in the RCT will be enrolled into the OBS arm. All participants (~1200 PAYA-CS) will also be enrolled into CPTP for life-long follow-up for CVD.

Interventions: **CORE** group will receive high intensity interval training (with CR facility, 2x/week) and home-based aerobic exercise (1x/week) with risk factor modification based on Canadian Guidelines for 6 months, and long-term exercise behaviour support through ActiveMatch.ca for 2 years. **SUPPORT** group will only receive long-term exercise behaviour support.

Outcomes: VO_{2peak} (via symptom limited cardiopulmonary exercise tests (CPET)), measures of S_BHF, CVD risk factor control, and patient report HrQoL.

Primary efficacy endpoint: Change in VO_{2peak} from baseline to 6 months between CORE and SUPPORT. **Secondary efficacy endpoints:** Change in measures of S_BHF, CVD risk factor control, and patient report HrQoL from baseline to 6, 12, and 24 months and VO_{2peak} at 12 and 24 months between CORE and SUPPORT. The outcomes will also be compared with OBS at baseline and T3. ***Analyses***: Multiple linear regression adjusted for baseline VO_{2peak}, age, time since cancer treatment completion and sex as covariates. Linear mixed effect models will be used for continuous secondary endpoints.

Implications: This study will determine whether ***CORE*** (1) should become a component of care in PAYA-CS with S_BHF, (2) can be delivered within existing CR programs, and (3) can reduce long-term risk of CVD.

Quan, May Lynn
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Preparing to survive: Improving outcomes for young women with breast cancer

Women aged ≤40 with breast cancer experience poorer outcomes, have a wide spectrum of supportive needs and face unique survivorship issues compared to their older counterparts. Research and supports are lacking for this population who comprise approximately 5.4% of all women diagnosed with breast cancer. To address this, we created RUBY (Reducing the bUrden of Breast cancer in Young women), one of the world's largest prospective cohorts of women with young-onset breast cancer. To date, we have enrolled over 1000 women from 32 sites across Canada *at the time of cancer diagnosis* following them through treatment and into the survivorship period. Through RUBY, we have identified unique survivorship gaps, including anxiety, depression and marital distress at diagnosis and well beyond. Specific, accessible interventions are required for these women, but are currently lacking. ICAN Manage Cancer, is a self-management, on-line intervention for patients with cancer designed to address comprehensive survivorship issues at diagnosis and beyond. Key areas of need include regaining balance/dealing with diagnosis, coping with treatment and side-effects, management of anxiety and depression, fatigue management, sexuality and relationships. The ICAN Manage Cancer intervention uses established behaviour change techniques to build self-management skills, however does not focus on the specific needs of young women. Thus, we will modify the ICAN intervention in collaboration with young onset survivors to develop the ICAN-RUBY self-management tool, and will then test the tool for effectiveness. We are uniquely positioned to develop this tool to address the unmet needs of young women with breast cancer (YWBC), given our direct knowledge of gaps identified to date from existing RUBY cohort, the established RUBY study infrastructure with a proven track record of recruitment, and our group of patient stakeholders.

Objectives:

1.To understand the psychosocial needs of YWBC embarking on cancer treatment

2.To co-develop the ICAN-RUBY self-management tool to support the specific needs of YWBC from the time of diagnosis, through treatment and into the survivorship period

3.To compare levels of anxiety, depression and self-efficacy post treatment, 12 and 24 months in YWBC who receive the ICAN-RUBY self-management tool versus usual care

Methods:

Phase 1: ICAN-RUBY

Co-Development. We will use qualitative methods and the results from 1000 current RUBY participants to identify the needs of YWBC at diagnosis, through treatment and into survivorship. Under an iKT framework, involving RUBY survivors and family, patient groups, and clinicians throughout, we will modify the generic ICAN Manage Cancer intervention to meet identified unmet needs of YWBC, creating ICAN-RUBY

Phase 2: ICAN-RUBY randomized registry trial. We will conduct a randomized controlled trial of the ICAN-RUBY intervention compared to usual care using up to 32 existing RUBY sites across Canada. 280 women will be recruited at enrolment into the RUBY cohort and randomized before first treatment. The primary outcome measure will be multiple psycho-social domains using patient reported outcome (PRO) instruments currently obtained as a core component of RUBY. All patient factors, tumour characteristics, treatments and PROs will be collected at baseline and 1-year post diagnosis as per the current RUBY protocol.

Significance and Impact: YWBC have unique survivorship needs and psychosocial functioning is compromised. Very little research has been directed at this group of women, and tailored interventions to address their unique needs are non-existent. Working with patients, clinicians, policy makers and advocacy members we will prioritize unmet needs to co-develop and evaluate an accessible intervention to meet those needs. If successful, we are positioned to implement ICAN-RUBY immediately through the existing RUBY network.